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FIBROSARCOMA ARISING IN THE HEMATONEPHROTIC SAC OF THE LOWER DIVISION OF A DOUBLE KIDNEY

FRED K. GARVEY, WAYNE A. CLINE AND C. C. CARPENTER

From the Department of Surgery, Division of Urology, Bowman Gray School of Medicine of Wake Forest College Winston-Salem, N. C. and the Department of Pathology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Sarcoma of the kidney is a comparatively rare tumor, particularly if adenomyosarcomas (Wilms tumors) and anaplastic carcinomas are excluded. We have recently seen a case of fibrosarcoma arising in the wall of a hematonephrotic sac in a double kidney. A review of the literature has brought to light only one comparable case.

CASE REPORT

A 24 year old white woman was seen in the office of one of us (F. K. G.) on June 16, 1948. The patient had been married 13 months and had had no pregnancies. She stated that within the first month after marriage she began having recurrent attacks of cystitis, characterized by frequency, dysuria, and occasional hematuria. These attacks which were apparently related to sexual activity would subside following the use of sulfonamides, but would recur. There had been no symptoms related to the upper urinary tract, and no chills or fever.

Physical examination, including examination of the abdomen and pelvis, was negative. A catheterized specimen of urine contained an occasional red and white blood cell. A cysto-urethroscopic examination showed some edema of the vesical neck. The urethra admitted a 24 F panendoscope with difficulty. Dilatation of the urethra was performed and therapy with mandelamine tablets and sandalwood oil was begun.

The patient was seen again in June and July and each time showed definite improvement. The urethra was dilated to admit a 30 F sound on each of these visits.

On January 19, 1949, the patient returned complaining of dull, aching pain and burning in the right upper quadrant, and stated that she had noticed a mass there. She had had nausea and vomiting with anorexia and had lost 10 pounds in weight recently. She had also noticed transitory attacks of pain in the right flank region every day or two for 2 months. The mass had not been tender, but she thought it had grown within the past few weeks. There was no history of renal stones, chills, or fever.

Examination of the abdomen revealed a large, smooth, round mass in the upper right quadrant. On palpation this was moved with respiration. It was nontender and felt to be rather firm, but somewhat cystic. Only one mass was felt, and the remainder of the abdominal examination was negative. Catheterized specimen of urine was negative.

On cystoscopy a No. 5 catheter passed easily to the left renal pelvis and drained normally. A ureteral orifice was seen on the right which admitted with difficulty a filiform bougie; this was dilated until a No. 3 catheter could be passed about two thirds of the way to the kidney. Iodide was injected with the patient's head lowered, and an x-ray showed almost no dye in the ureter and none in the renal pelvis; with the ureteral catheter deviated laterally (fig. 1, *A*). A left pyelogram revealed moderate hydronephrosis.

The diagnosis was possible hydronephrosis, cyst, or tumor of the right kidney. The patient was hospitalized.

Physical examination showed the temperature to be 98.6 F, the pulse 86, respiration 20, blood pressure 110 systolic and 68 diastolic. The positive findings which were limited to the abdomen are described above.

Examination of the blood showed 13.3 gm. hemoglobin, 4,180,000 red blood cells, 6,500 white blood cells, with a normal differential count. A catheterized specimen of urine was yellow and cloudy with an alkaline reaction and a specific gravity of 1.010. It contained no albumin or sugar and microscopic examination showed 1-2 white blood cells and 9-10 red blood cells per high power field. The urine culture revealed staphylococci, coagulose positive, probably pathogenic. The phenolsulfonphthalein test for kidney function showed 15 per cent excretion in the first 30 minutes, 10 per cent in the second 30 minutes, 5 per cent in the third, and 5 per cent in the fourth, a total of 35 per cent in 2 hours. The nonprotein nitrogen was 32 mg. per cent per 100 cc.

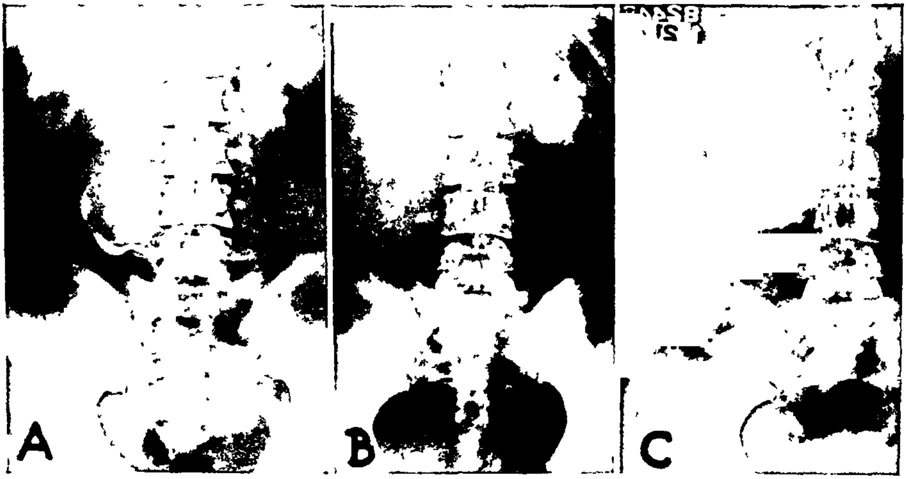

FIG. 1. *A*, retrograde pyelograms showing right ureteral catheter in place deviated laterally by large mass. *B*, excretory urogram, 30 minute film, showing displacement upward and medially of right renal pelvis by large mass. *C*, cystic mass of right flank injected with dye

On the day following admission a plain film of the abdomen and excretory urograms were made. The report was as follows: "On the plain film of the abdomen, the left kidney and psoas shadow appear normal in outline. There is a large, soft tissue mass occupying the right abdomen extending down to about 2 cm. above the iliac crest. On the excretory urogram, one sees dilatation of the left kidney pelvis. The calyces on the left show normal cupping. This dilatation of the pelvis has the appearance of being produced by anomalous vessels. There also appears to be abnormal rotation of that kidney. Only a small portion of the right kidney pelvis and upper calyx are visualized. This is probably due to rotation and anomalous vessels producing a block at the ureteropelvic junction. The soft tissue mass on the right is probably produced by a huge hydronephrosis (fig. 1, *B*). A renal cyst or renal neoplasm cannot be ruled out."

On the third hospital day following the aspiration of bloody fluid, dye was injected into the cystic mass, and a roentgenogram was made. A large cavity was revealed measuring 12 by 16 cm. (fig. 1, *C*). Our impression then was probable cyst of the lower pole of the right kidney. The patient was immediately taken to the operating room.

A long, curved, right loin incision was made extending nearly to the umbilicus. The overlying muscles were divided, and Gerota's fascia was entered. A large, tense, brownish, elastic mass was encountered which measured approximately 15 to 18 cm. in diameter. Two ureters were discovered, one leading to the large mass, the other to what was apparently a small, normal upper half of a double right kidney. The ureter which was attached to the hydronephrotic portion was cut and tied with No. 1 chromic catgut. Unfortunately, it was not possible to demonstrate where the ureter bifurcated.

There were a few adhesions binding down the large mass. These were separated, cut and tied. The pedicle was clamped with two pedicle clamps, cut, and tied with a single suture of No. 3 chromic catgut. The mass was delivered up into the wound, the upper portion of the kidney seemed small, but otherwise normal. The hydronephrotic portion was separated from the normal upper portion. It extended somewhat into the substance of the upper portion, but was shelled out without too much difficulty. The ureter of the upper portion appeared normal, as did the pelvis. There was some bleeding from the raw surface after the lower half of the kidney had been removed. This was controlled by three mattress sutures of No. 0 plain catgut. Bleeding was well controlled at the end of the procedure.

Gerota's fascia was brought over and sutured to the quadratus lumborum to give the kidney some support. Two Penrose drains were placed in the fossa, and the wound was closed in layers. The patient withstood the procedure well.

The patient was given penicillin and sulfadiazine prophylactically. Her postoperative course was uncomplicated and she was discharged on the ninth postoperative day in good condition.

The gross specimen (fig. 2) consisted of a large cystic mass which was of a bluish-red color and measured 12 by 14 by 12 cm. To one side of the mass an area of increased density was noted which measured approximately 7 by 2 cm; upon sectioning, this proved to be kidney. Arising from the external surface of the cystic mass was a small band of tissue 5 cm. in length, which was thought to represent the ureter. Further examination revealed a lumen which was patent to the cystic mass, where it ended blindly.

Upon being opened, the cyst was found to be filled with a dark, reddish-brown material which resembled old blood. The lining of the cyst was smooth except in one point. Here a friable, irregular, dark red mass was noted which measured 5 by 1.5 cm. (fig. 3). The wall of the cyst was very thin approximately

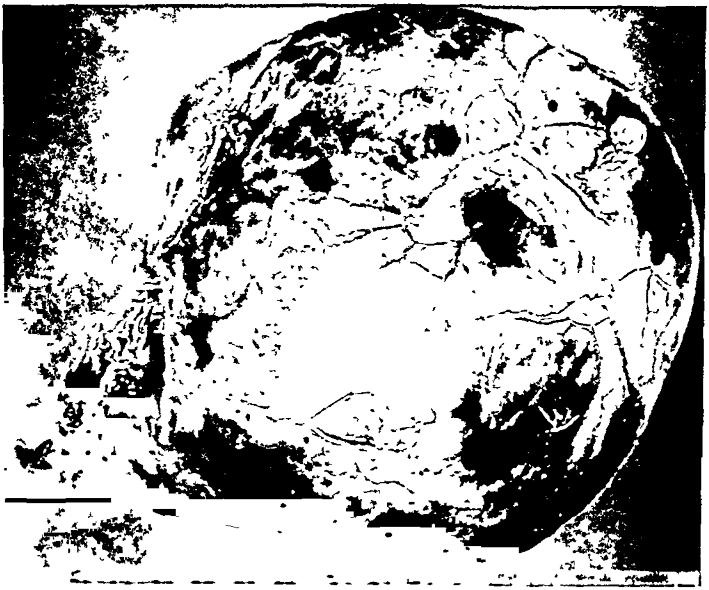

FIG. 2. Gross surgical specimen. Note ureter in left upper corner of mass

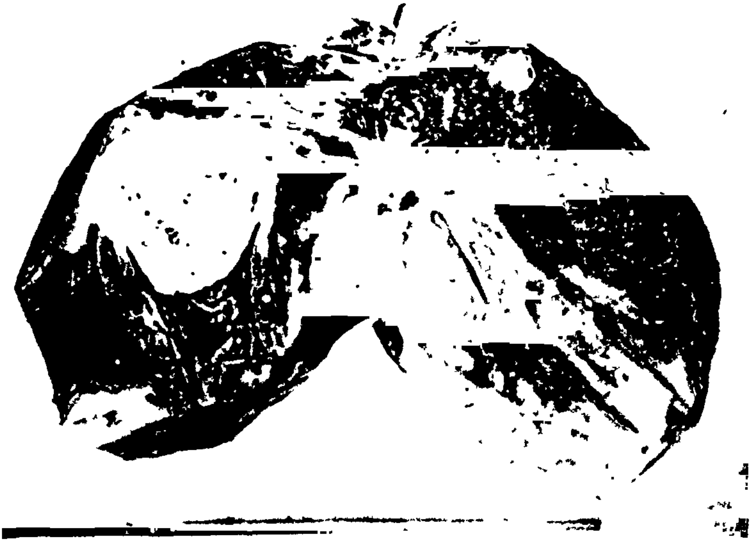

FIG. 3 Gross specimen opened, showing friable "blood clot" adherent to wall of hematonephrotic sac

0.1 cm. in thickness. In that part of the cyst which was adjacent to the kidney, a little irregularity in the contour of the wall was noted. This probably represented compressed, dilated calyces and flattened pyramids.

Microscopic sections: The thin portion of the cyst wall, which constituted the major portion of the cyst, was lined by a single layer of flattened epithelial cells (fig. 4). As the intracystic mass was approached, the epithelium became stratified and was transformed into the transitional variety. Beneath the epithelium a lamina propria was noted which was composed of relatively acellular, collagenous

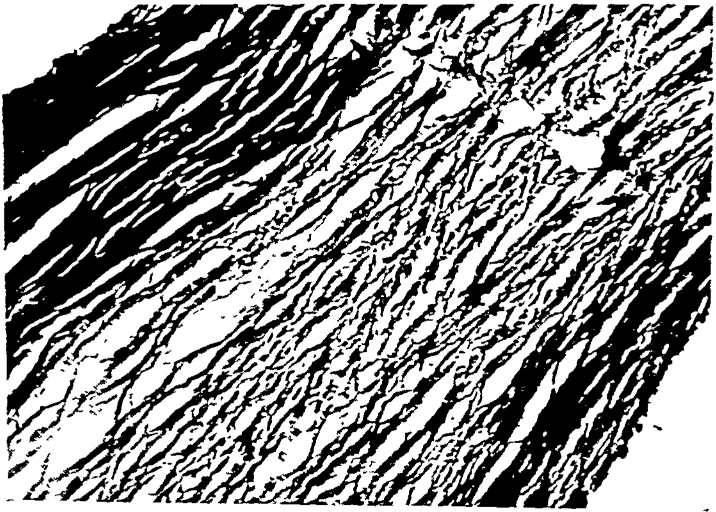

FIG. 4. High power photomicrograph of thinnest portion of wall of sac revealing eosinophilic, hyalinized, acellular fibrous tissue and atrophic smooth muscles.

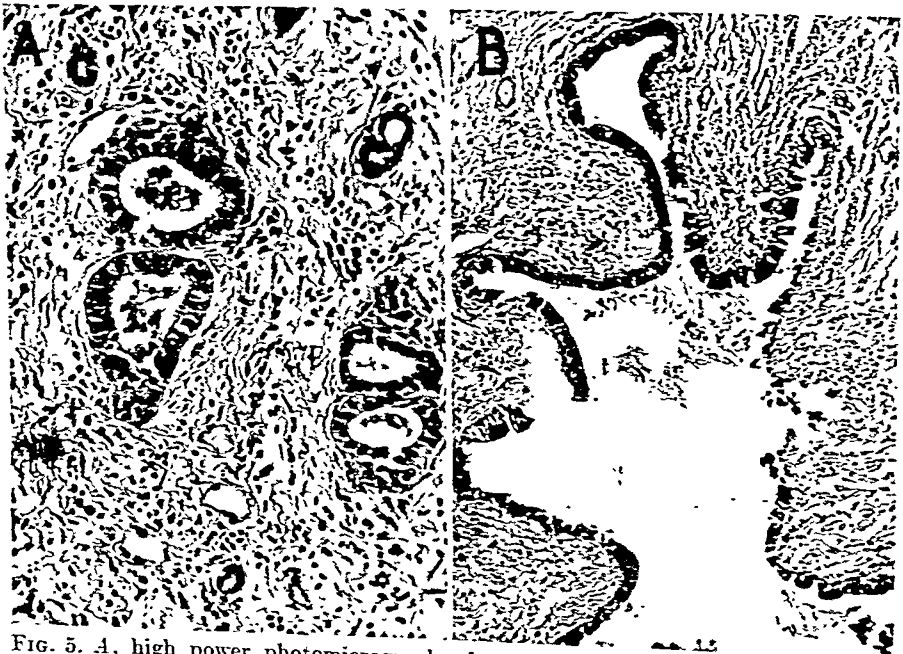

FIG. 5. *A*, high power photomicrograph of a portion of wall showing dilated and atrophic renal tubules in a loose fibrotic tissue stroma invaded by moderate number of mononuclear cells. *B*, low power photomicrograph showing ureter of hydronephrotic sac.

connective tissue. Atrophic but well defined layers of smooth muscle cells were seen immediately adjacent to this.

The kidney tissue opposite the cystic structure showed dilated tubules and an occasional glomerulus, all that remained of the renal parenchyma (fig. 5, *A*). These structures were surrounded by large amounts of fibrous tissue which were infiltrated with inflammatory cells, predominantly of the chronic variety. In this same vicinity, numerous phagocytic cells, heavily loaded with hemosiderin and arranged singly and in sheets, were noted.

Section through the ureter revealed no pathologic change (fig. 5, *B*).

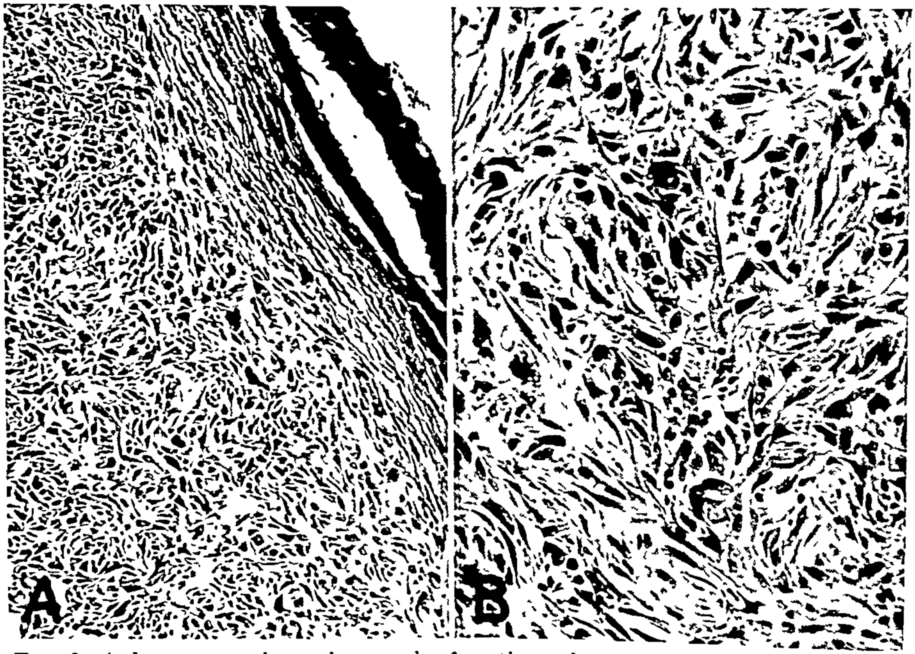

FIG. 6. *A*, low power photomicrograph of section taken through wall at what grossly resembled "friable, dark red blood clot," showing base of tumor *B*, high power photomicrograph showing tumor.

Sections through the intracystic hemorrhagic mass showed it to be continuous with lamina propria of the pelvis of the kidney. The normal connective tissue in this area was abruptly replaced by actively proliferative fibroblasts which were hyperchromatic and varied greatly in size and shape and staining characteristics (fig. 6, *A* and *B*). Mitotic figures were present in moderate numbers, and an occasional tumor giant cell was seen. The stroma was collagenous in character, and varied in amount in different localities. Tumor tissue was not demonstrated in other portions of this cyst, and the tumor did not invade the surrounding structures.

Final diagnosis: Double right kidney; atresia of the ureteropelvic junction in the lower portion of the double kidney; hydronephrosis, with almost complete atrophy of the adjacent renal parenchyma; fibrosarcoma in the wall of a hematonephrotic sac.

On February 14, 1949, the patient returned for her first check-up. She had gained weight, and had no complaints. Since the point of bifurcation of the ureter had not been demonstrated at operation, an attempt was made to catheterize the right ureteral orifice. The meatus was so small that, in spite of repeated attempts, catheterization was impossible. Urinalysis was negative on this visit.

On February 23, 1949, excretory urograms were made. There was prompt excretion of the dye from both the left kidney and the remaining division of the right kidney. The right renal pelvis was small and showed no evidence of hydronephrosis. Unfortunately, these films failed to show the ureters. Catheterization of the right ureteral orifice was again attempted, but was unsuccessful. Indigo carmine was injected intravenously, but on cystoscopy failed to reveal a second ureteral orifice, and no ectopic orifice was demonstrated. The retrograde pyelogram of the left kidney revealed moderate hydronephrosis, probably due to anomalous vessels.

On February 24 the patient returned with chills and fever 102 F, left flank pain, and nausea and vomiting. She was again admitted to the hospital.

Physical examination revealed a well healed right loin incision and moderate bilateral tenderness in the costovertebral angles.

Laboratory findings on this admission were as follows: A blood count showed 12.2 gm. of hemoglobin, 3,950,000 red blood cells, and 24,600 white blood cells with a shift to the left in the Schilling hemogram. The urine was cloudy and yellow with a specific gravity of 1.011, a trace of albumin and no sugar. Microscopic examination showed 12–15 white blood cells and 5–10 red blood cells per high power field. A chest film was negative.

In spite of treatment with penicillin, 1 cc duracillin daily, and sulfadiazine 2.0 gm. daily, the patient continued to have daily elevations of temperature to 102 F until the third hospital day, when dihydrostreptomycin was started. Her temperature fell to normal in 24 hours, and she rapidly recovered. She was discharged on the eighth hospital day.

It is far too early to talk of a cure. However, from the pathologic standpoint the tumor was confined to a small area, and certainly appeared to have been completely removed. There is no clinical evidence of tumor elsewhere. We still have not demonstrated the bifurcation of the ureter, and are at a loss to explain the tight ureteral orifice on the right side; possibly this represents another congenital abnormality. In a short time, we expect to evaluate the left kidney more fully and attempt to correct the cause of obstruction on this side. It is hoped that in the near future a more adequate follow-up study may be reported.

ADDENDUM

Cystoscopy on May 27, 1949 revealed a second ureteral orifice on the right side located medially but not in the usual position for reduplication. This, therefore, proved that there was a complete reduplication of the ureter with two ureteral orifices in the bladder on the right side.

In October 1949, the patient returned complaining of right costovertebral angle pain radiating to right lower quadrant and right lower extremity. All studies were negative. A right pyelo-ureterogram showed no obstruction to drainage. Because of the persistence of the pain, a right renal exploration was done revealing necrotic tumor tissue in the region of the right psoas muscle. Pathologic sections revealed the same type of tumor as described in the original report. The remaining portion of the right kidney was removed and on careful sections failed to reveal any tumor. Palliative deep x-ray therapy was given. The patient expired at home on December 31, 1949.

REFERENCE

RALPH, F. G.: Sarcoma of renal pelvis associated with hydronephrosis. Brit. J. Surg., **13**: 190, 1925.

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RENAL ANGIOMA: SUSPECTED BILATERAL INVOLVEMENT

BERNARD E. PALETZ AND GEORGE SEWELL

Renal hemangioma is a relatively rare condition. In a review of this literature by Lazarus and Marks, only 70 cases were found. It is very probable that many more cases have been recognized but not reported. One such instance occurred in this hospital in 1943 for which a nephrectomy had been performed.

In all cases reported, involvement of only one kidney has been mentioned. The following case offers two unusual features which have not been reported. First, there is strong evidence to suspect that both kidneys were affected; second, hemorrhage subsided following deep x-ray therapy.

CASE REPORTS

A. M., a 21 year old well nourished Negro, was admitted to Receiving Hospital on October 31, 1946 with the history of passing dark blood in his urine for 2 days. Bleeding was profuse and unaccompanied by pain, frequency, dysuria, chills or fever. Hematuria of the same character was first noticed 10 years previously and cleared up in several days. This bleeding recurred numerous times in succeeding years on an average of once a year. Episodes lasted from one day to a week. Patient was operated transurethrally in 1945 at which time he was told a "bladder tumor" was removed. There was no history of weight loss, night sweats, cough or hemoptysis. Past history was irrelevant other than that a brother died in childhood of "kidney trouble."

Temperature and pulse were normal on admission. Physical examination was entirely negative. Kidneys were not palpable.

Laboratory studies showed grossly bloody urine containing thick clots. Nonprotein nitrogen was 37, hemoglobin 10.5 gm., white blood cells 4,150, containing 58 neutrophiles, 26 lymphocytes, 9 monocytes, 6 eosinophiles and 1 basophile.

Cystoscopy showed that the bladder was filled with soft jelly-like clots. After evacuation of the clots the bladder wall appeared normal. Spurts of blood were seen coming from the right ureteral orifice but none from the left. Catheters were passed to both kidney pelves with ease. There was a rapid drip of grossly bloody urine from the right kidney. Specimen from the left kidney was crystal clear. Indigo carmine appeared from both sides in 4 minutes. Pyelographic studies showed a normal pelvis and normal calyces on the left. On the right side the middle and lower calyces were normal but the superior major calyx and its two branches showed generalized dilatation and some irregularity. Microscopic study showed clotted blood from the right while that from the left kidney was negative.

The hematuria persisted. Cystoscopy was repeated November 4, 1946. The findings were identical to those described above. There were no changes in the pyelograms. X-ray of the chest was negative. No acid fast organisms were found in the stained sediment of three 24 hour urine specimens. The hemoglobin

Read at meeting of Detroit Urological Society, November 12, 1947.

commenced dropping after several days necessitating the administration of three 500 cc blood transfusions. A tentative diagnosis of hemangioma of the right kidney was made and nephrectomy advised as a life saving measure.

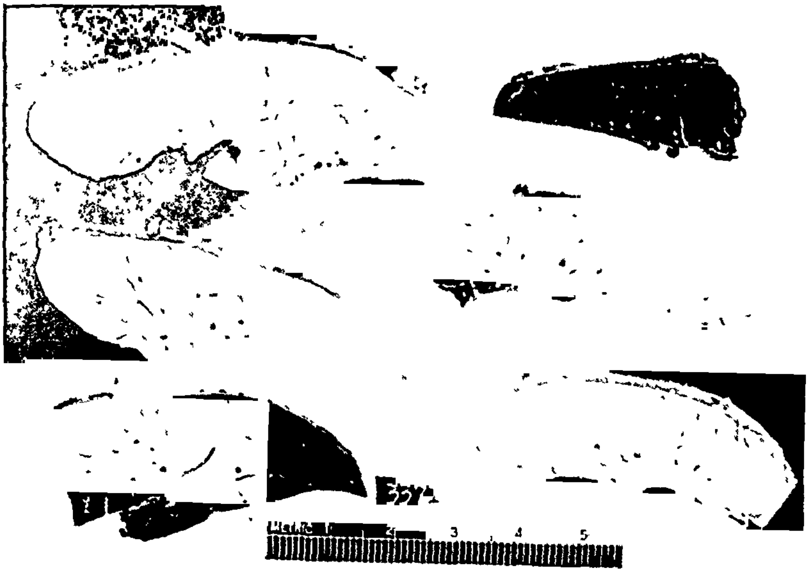

Fig. 1. Gross specimen

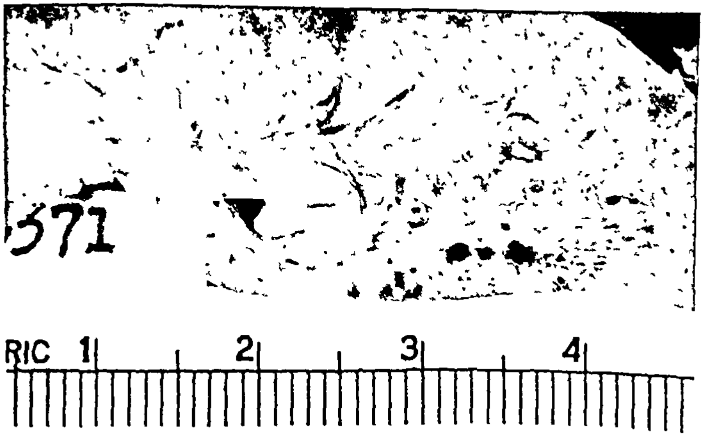

Fig 2 Close-up through renal pelvis

On November 11, 1946, the kidney was easily exposed from its bed and brought to the surface. It appeared grossly normal. Removal was accomplished without difficulty.

Pathological report (Dr. O. A. Brines, head of the Department of Pathology, Receiving Hospital and professor of pathology, Wayne University College of Medicine): "The gross specimen is a right kidney weighing 180 gm. and measuring 11 by 6 by 4 cm. The external surface is reddish-purple in color and smooth.

The capsule presents a few fibrous adhesions but strips with ease, having a smooth surface. On cut section the parenchyma is reddish-brown. The cortex measures 8 mm. in thickness and is distinct from the medulla. There is no dilatation of the ureter, pelvis or calyces. Throughout the medulla there are tiny scattered spots which may represent recent hemorrhage. At the pyramids a small amount of red blood can be seen appearing to be present in the tubules, and this same bright red blood can be seen in the distribution of the collecting tubules.

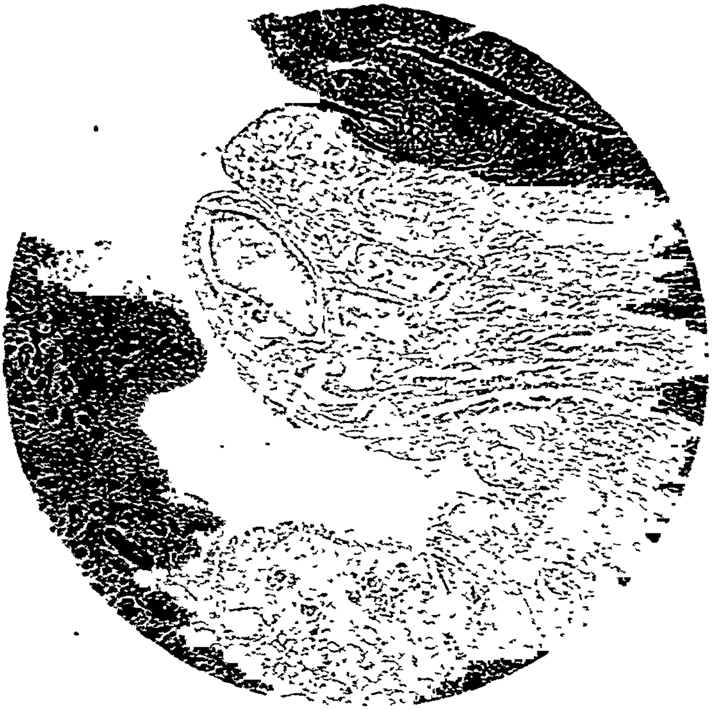

FIG. 3. Section through a papilla

"Microscopic: The glomeruli and tubules are relatively normal. Scattered throughout the renal parenchyma and particularly conspicuous in the medulla are seen numerous dilated vascular spaces. Most of the spaces contain fresh blood and are lined with a single layer of endothelial cells. The spaces vary greatly in size from 25 mu. to 300 mu. In some areas the vascular channels appear as capillaries whereas in other areas a definite cavernous pattern is apparent. In some places rupture has occurred with resultant hemorrhage. Nowhere is there proliferation of endothelial cells suggestive of hemangio-endothelioma (a malignant tumor). Between the vascular spaces a scanty stroma is present. Diagnosis: hemangioma, multiple, diffuse right kidney." See figures 1, 2, 3, 4.

Convalescence was uneventful and the patient was discharged on the fourteenth postoperative day.

The patient was readmitted on December 24, 1946. He stated that he started bleeding 3 days after he left the hospital. Bleeding had been continuous since. His urine was grossly bloody on admission. Cystoscopic examination was performed 2 days later and repeated in 6 days and 8 days. On all three occasions urine obtained from the remaining left kidney was devoid of microscopic blood and the pyelograms were negative. The patient was discharged on January 3, 1947 with clear urine.

The third admission was January 21, 1947 because of a recurrence of the hematuria. On cystoscopic examination the bladder was full of clots. Spurts of practically pure blood could be seen coming from the left ureteral orifice. The pyelogram was normal. At this time it was strongly suspected that an identical pathological process existed in the remaining kidney that had been found on the right following nephrectomy. Hematuria persisted at an alarming rate. Patient was sustained by repeated blood transfusions receiving seven 500 cc units. The roentgenologists were consulted as to the advisability of radiation to the left kidney in an attempt to slacken the bleeding. Without previous experience in such a case the following therapy was administered. The left kidney was treated through two ports, one anterior and one posterior, each 12 by 20 cm. in size. The fields were treated on each of two consecutive days (February 7 and 8, 1947); 200 r (air) were given per field per day. The quality of radiation was 200 KVP,

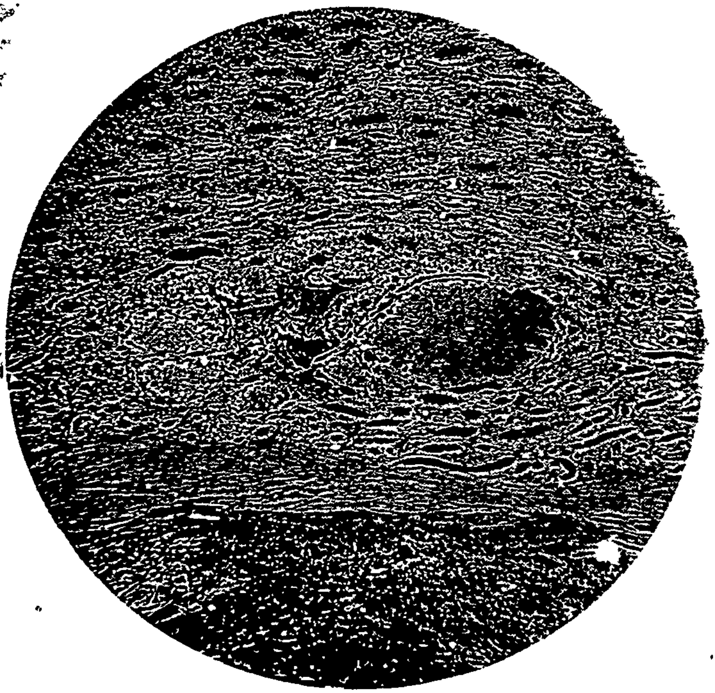

Fig. 4. Section through medulla in region of hilus

$\frac{1}{2}$ mm Cu + 4 mm AL, and HVL of 1.12 mm Cu. The target skin distance was 50 cm. and the intensity of radiation was 33.8 r (air) per minute. The depth of the tumor was estimated; and from depth dose and cumulation dose charts, it was deduced that the kidney received a cumulative dose of 435 r.

The roentgenologist estimated that it would take approximately 6 weeks for the radiation to show its effects.

Cystoscopic examination was repeated February 3, 1947. As before, blood was seen spurting from the left ureteral orifice; a normal pyelogram was obtained.

On February 27, 1947 and March 6, 1947 the kidney pelvis was irrigated thoroughly with 1:1000 silver nitrate solution. Bleeding persisted as profusely as ever. The blood urea throughout his hospital stay did not rise above 31.

On March 12, 1947 the bleeding ceased very suddenly. Microscopic examination the following day showed only an occasional red blood cell. He was discharged from the hospital March 14, 1947, at his own request, symptom free.

His urine has remained clear on follow-up examination to present date.

DISCUSSION

The character of the bleeding seen from the left kidney following right nephrectomy was identical to that seen on the right prior to surgery. In view of the absence of any positive physical, laboratory or pyelographic findings, plus the congenital nature of the process, it seems reasonable to assume that an identical pathological process exists in the remaining kidney. The patient will be followed, but unless he has a recurrence of his symptoms that cannot be controlled, positive microscopic proof of a bilateral involvement will have to wait the passage of years. One does not feel justified in exploring the remaining kidney.

The apparent response to x-ray therapy was particularly interesting. As a last resort the patient was referred to the roentgenologist. Without previous experience on which to gauge the dosage, a dose was administered that would ordinarily be given for a hemangioma on the skin surface. He predicted that it would take approximately 6 weeks for the therapy to make its effects known. Bleeding ceased on approximately the fifth week. It is not believed that washing the renal pelvis with silver nitrate solution was any factor in the cessation of bleeding.

The treatment of hemangiomas of the kidney is nephrectomy. It seems wisest never to explore a kidney for hematuria unless prepared to remove it. Lesions may be so small that they might be easily overlooked on gross inspection. Furthermore the angioma might be multiple or diffusely scattered throughout the kidney as found in this case. In view of the varied histologic picture, heminephrectomy or resection of a papilla might not ensure its entire extirpation. If the remaining kidney cannot support life, roentgen therapy offers a possibility for controlling hemorrhage.

SUMMARY

A case of hemangioma of the kidney is presented in which the evidence strongly pointed to bilateral involvement and in which the lesion was diffusely scattered throughout the kidney parenchyma.

Roentgen therapy is offered as a means of controlling renal hemorrhage when nephrectomy is contraindicated.

Renal hemangiomas are probably not as rare as reported and may explain many cases of undiagnosed hematuria.

Indebtedness is acknowledged to Dr. James Lofstrom, Department of Radiology, St. Mary's Hospital, Detroit.

REFERENCE

LAZARUS, J. A. AND MARKS, M. S.: Renal hemangioma. Urol. and Cutan. Rev., **51: 500–509,** 1947.

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HEMANGIOMA OF THE KIDNEY

ARTHUR J. BUTT AND JOSEPH Q. PERRY

Hemangioma of the kidney is considered a rare disease. It is omitted from several current classifications of renal tumor and until recently little cognizance has been taken of this condition. Virchow described the first case from an autopsy specimen in 1867, and it was probably first recognized clinically in 1903 by Fenwick. Riley and Swann made a comprehensive review of the subject up to 1941, which included only 36 authentic cases, and they added 1 personally observed case. Since that time, 17 additional cases have been reported, and the case herein presented brings the total to 55.

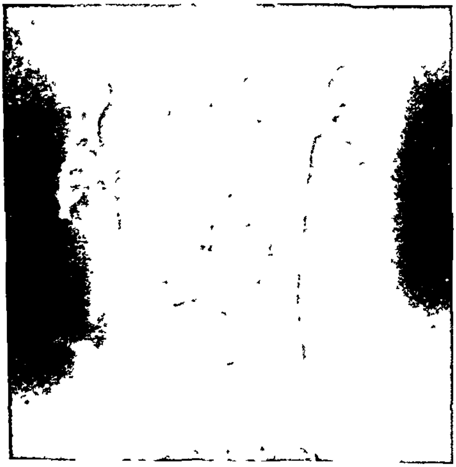
The congenital origin of the great majority of hemangiomas points strongly in favor of tissue predisposition as a prominent factor in their genesis. Virchow believed that angiomas formed from imperfectly formed vessels. Rokitansky considered that many angiomas represented simple hypertrophy of vascular segments without neoplastic growth. Thoma believed that much of the growth of angiomas was due to mechanical factors. Increase in blood pressure and loss of support to the vessel walls from changes in the surrounding tissues are thought to excite new growth of vessels while increased rapidity of blood flow favors elongation and dilatation of the walls.

Renal vascular tumors may be classified as telangiectasis and varix; capillary hemangioma and plexiform hemangioma; cavernous hemangioma; hemangiosarcoma, and hemangioblastoma. Hemangiomas may vary from pin point size to massive forms. Due to the insignificant size of the lesion in most cases, it may be easily overlooked in post-mortem examinations, especially in those which give no evidence of renal symptoms. Even when the kidney is removed surgically, the tumor may be difficult to find.

Hemangiomas have a deep reddish color, and may be located in the cortex, medulla, at the tip of a papilla or subepithelially in the pelvis. The tumor usually invades the surrounding kidney substance but occasionally it is encapsulated. Microscopically these tumors have all the features of dilated blood-filled spaces lined with epithelium. Usually there is a more or less fibrous stroma which sometimes is condensed to form a capsule. Walls of the vascular spaces may be single layered or they may contain layers of elastic tissue fibers. The vessel wall may be so thick that the term arterial angioma can be applied.

Generally, benign renal tumors are asymptomatic and give rise to symptoms only when of unusual size. In contrast, renal hemangiomas have as a cardinal symptom, hematuria. It may occur as slight or intermittent bleeding extending over a period of months or years or may be so profound that it gravely endangers life from exsanguination. In several of the cases reported, operation was performed to control dangerous hemorrhage and was considered a life saving measure. Pain is not a constant factor, but occasionally in the larger tumors, pain from pressure may be the first symptom noticed. Usually, the pain is colicky in nature, is accompanied by hematuria, and is due to passage of blood clots down the ureter. The average age of onset of symptoms is under 40 years, which is in contrast to the more common age for malignant tumors. There are no characteristic radiological features of renal hemangiomas. The presence of hematuria, especially over a long period of time, with absence of significant x-ray evidence as to the cause, is suggestive of benign vascular renal tumor. Papanicolaou and others have demonstrated that malignant tumors of the urinary tract may be determined by examining the urinary sediment. This method of study is of value when a differential diagnosis of renal tumor is being made. Congenital tumors are so frequently multiple that one should suspect involvement of internal organs when there are hemangiomas on the surface of the body.

The treatment of this type of renal tumor in most instances is nephrectomy. More conservative measures such as heminephrectomy or calyectomy may be indicated when the tumor is at one pole of the kidney, when it is combined with generalized cutaneous hemangiomatosis which may indicate bilateral renal involvement, or when there is disease of the opposite kidney. Hamm and Rappoport have recently reported partial resection of the kidney to remove hemangiomas.



CASE REPORT

September 23, 1948, Mrs. F. Q., aged 60, was referred for urological consultation because of recurrent hematuria. In 1933, she first complained of a mild aching sensation of fullness in the left upper quadrant and in the left flank. Several other physicians examined her and found microscopic blood in the urine; however, no further urological examination was performed. Following this, at irregular intervals, she had recurrent attacks of pain in the left flank. In 1937, she first passed grossly bloody urine which contained numerous tubular blood clots, and since then gross hematuria has recurred intermittently. She noticed that it was more profuse after long or rough automobile rides. She also observed that during the first part of the day the urine was usually clear, but in the afternoon and the evening the urine was grossly bloody. Her husband died of pulmonary tuberculosis. One brother died of carcinoma of the bladder, and one aunt died of carcinoma of the colon.

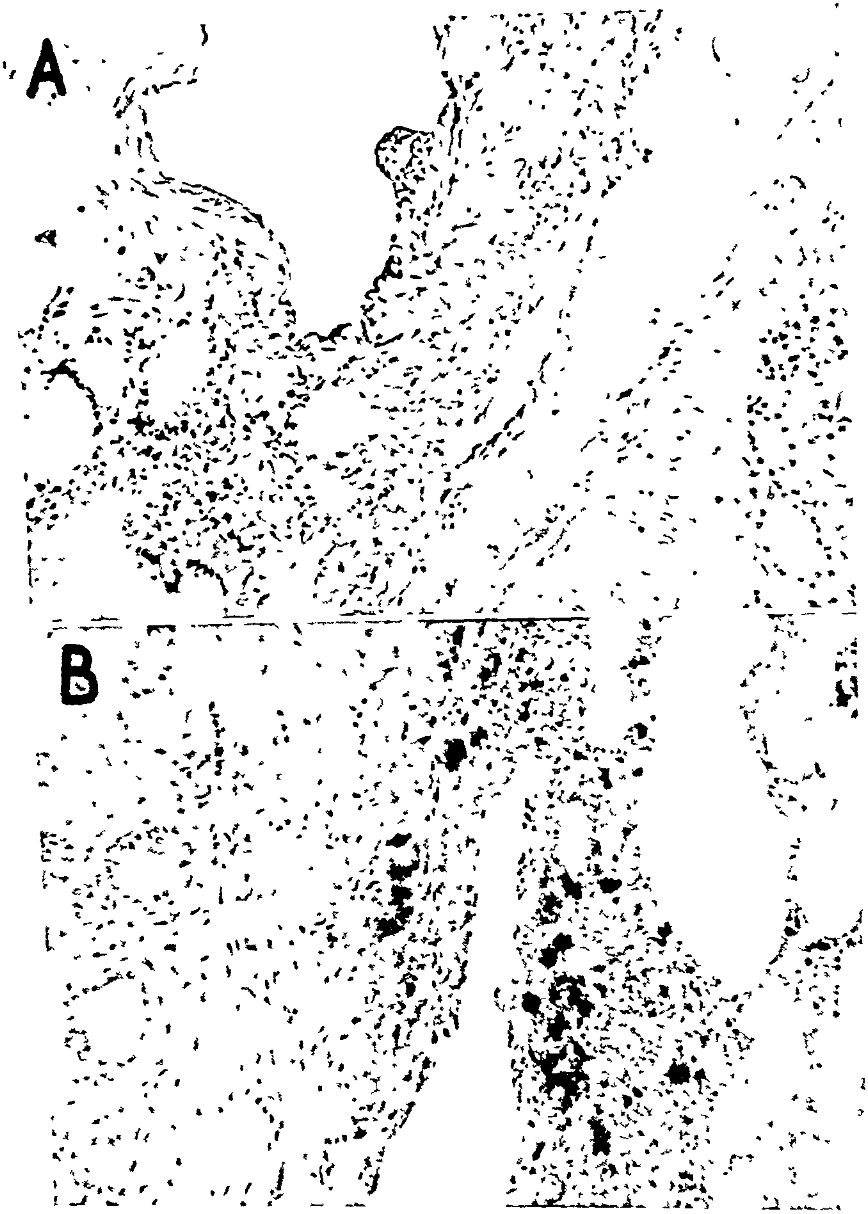


Fig 2 *A*, low power (× 100) *B*, high power (× 450)

Physical examination revealed a pale, underweight, chronically ill-looking woman. The heart and lungs were within normal limits Blood pressure was 180 systolic, 80 diastolic. The liver was palpable 3 cm. below the right costal margin. The kidneys were neither tender nor palpable. The urine was grossly bloody and contained numerous small clots. Urine culture revealed colon bacillus. Hemo-the ureter. The average age of onset of symptoms is under 40 years, which is in contrast to the more common age for malignant tumors. There are no characteristic radiological features of renal hemangiomas. The presence of hematuria, especially over a long period of time, with absence of significant x-ray evidence as to the cause, is suggestive of benign vascular renal tumor. Papanicolaou and others have demonstrated that malignant tumors of the urinary tract may be determined by examining the urinary sediment. This method of study is of value when a differential diagnosis of renal tumor is being made. Congenital tumors are so frequently multiple that one should suspect involvement of internal organs when there are hemangiomas on the surface of the body.

The treatment of this type of renal tumor in most instances is nephrectomy. More conservative measures such as heminephrectomy or calyectomy may be indicated when the tumor is at one pole of the kidney, when it is combined with generalized cutaneous hemangiomatosis which may indicate bilateral renal involvement, or when there is disease of the opposite kidney. Hamm and Rappoport have recently reported partial resection of the kidney to remove hemangiomas.

CASE REPORT

September 23, 1948, Mrs. F. Q., aged 60, was referred for urological consultation because of recurrent hematuria. In 1933, she first complained of a mild aching sensation of fullness in the left upper quadrant and in the left flank. Several other physicians examined her and found microscopic blood in the urine; however, no further urological examination was performed. Following this, at irregular intervals, she had recurrent attacks of pain in the left flank. In 1937, she first passed grossly bloody urine which contained numerous tubular blood clots, and since then gross hematuria has recurred intermittently. She noticed that it was more profuse after long or rough automobile rides. She also observed that during the first part of the day the urine was usually clear, but in the afternoon and the evening the urine was grossly bloody. Her husband died of pul-

REFERENCES

Bell, E. T.: J. Urol., **39**: 238-243, 1938.
Chenery, A. J. and Benson, A. H.: J. Urol., **39**: 164-166, 1948.
Daut, R. V. and McDonald, J. R.: Proc. Staff Meet. Mayo Clin., **22**: 382-386, 1947.
Dean, A. L. and McCarthy, W. D.: Trans. Am. Assoc. Genito-Urinary Surg. **33**: 1-9, 1941.
Dorman, H. N. and Fowler, H. A.: J. Urol., **55**: 348-357, 1946.
Farkas, K.: Virchow's Arch. f. path. Anat., **304**: 473, 1939.
Fenwick, H.: Clinical Cystoscopy. London, 1904.
Fukuda: Cited by Lutz, G.: Ztschr. f. urol. Chir., **17**: 93, 1925.
Hamm, F. C.: J. Urol., **55**: 143-148, 1946.
Heckel, N. J. and Penick, G. D.: J. Urol., **59**: 572, 1948.
Ipieus, P.: Arch. españ. urol., **3**: 211-216, 1947.
Judd, E. S. and Simon, H. E.: Surg., Gynec. and Obst., **46**: 711-713, 1928
Lownes, J. B., Baron, S. and Lipshutz, H.: J. Urol., **58**: 417-423, 1947.
MacKenzie, D. W. and Hawthorne, A. B.: J. Urol., **26**: 205-207, 1931.
McLean, E. H. and Mathews, T. J.: West J. Surg., **50**: 47-50, 1942.
Papanicolaou, G. N.: J. A. M. A., **131**: 372-378, 1946.
Papanicolaou, G. N.: J. Urol., **57**: 375-379, 1947.
Riley, A. and Swann, W. J.: Urol. and Cutan. Rev., **45**: 377-382, 1941.
Rappoport, A. E.: Arch. Path., **40**: 84-87, 1945.
Rives, H. F. and Pool, T. L.: J. A. M. A., **125**: 1187-1188, 1944.
Rottino, A. and Mohan, H.: J. Urol., **51**: 601-605, 1944.
Schmidlapp, C. J. and Marshall, V. F.: J. Urol., ***59****: 599-603, 1948.*
Shaheen, A. L., Cassano, C. and Lisa, J. R.: J. Urol., **51**: 597-600, 1944.
Swan, R. H. J.: Proc. Royal Soc. Med., **14**: 35, 1921.
Swan, R. H. and Balme, J.: Brit. J. Surg., **123**: 282-295, 1935-36;
Turkel, E. F.: J. Urol., **59**: 802-806, 1948.
Vallett, B. S.: Delaware State Med. J. **18**: 155-157, 1946.
White, E. W. and Braunstein, L. E.: J. Urol., **56**: 183-189, 1946;

globin, 58 per cent; red blood cells 2,900,000; white blood cells, within normal limits; nonprotein nitrogen was 32 mg. per cent; prothrombin time 90 per cent of normal.

An x-ray of the chest showed no abnormalities. Cystoscopic examination, July 12, 1948, revealed slight injection of the vesical mucosa and grossly bloody urine spurting from the left ureteral orifice. Indigo carmine appeared at the right orifice within 4 minutes in good concentration; left orifice, 5 minutes, good concentration. A plain x-ray and excretory urograms revealed a filling defect in the middle calyx of the left kidney. Retrograde pyelograms showed no change in the filling defect (fig. 1). Because of the long duration of symptoms, a tentative diagnosis of renal vascular tumor, probably benign, was made, and she was observed for a month, at the end of which time retrograde pyelograms showed no change from the previous x-rays. Six weeks after the first x-rays were made, retrograde pyelograms again revealed filling defect and no other appreciable change in the renal architecture. A diagnosis was made of benign renal tumor, blood vessel type.

The patient was admitted to the hospital on September 14, 1948. She was given two transfusions of 500 cc of blood, preoperatively. On September 18, 1948, a left nephrectomy was performed. The kidney was approached through a posterolumber incision. Grossly, the kidney appeared normal. Because of the persistent hematuria, the urographic findings, and the fact that the tumor was located adjacent to a middle calyx, the kidney was removed. The kidney measured 12 by 7 by 6.5 cm. and weighed 145 gm. Bisection revealed normal cortical and medullary portions within the upper and lower poles. In the midportion of the kidney there was a hemorrhagic tumor measuring 1.5 by 1 cm. which extended to the renal pelvis at the middle calyx. Microscopic examination revealed large and smaller blood spaces lined, as a rule, by a single layer of endothelium. Several of the larger cavernous spaces were completely obliterated by sclerosis, and this fibrous obliterating tissue was hyalinized. In some of the larger aberrant vessels, there were masses of blood pigment which was probably a result of hemorrhage of the angioma vessels. There was a diffuse infiltration of the lymphocytic cells about certain of the cavernous spaces (fig. 2). Convalescence was uneventful, and the patient was discharged from the hospital on the tenth day after the operation. Six months postoperatively she was free of symptoms and had gained 12 pounds.

SUMMARY

A case of renal hemangioma in which the diagnosis was made preoperatively is presented. If more exhaustive examinations of the kidneys are made, more cases of so-called essential hematuria may be found to be due to hemangioma. Study of urinary sediment for malignant cells may prove to be of great value in the differential diagnosis of benign and malignant urinary tract tumors. Conservative surgery such as resection of the part of the kidney containing the tumor may be carried out in some cases where a diagnosis of benign renal vascular tumor has been made.

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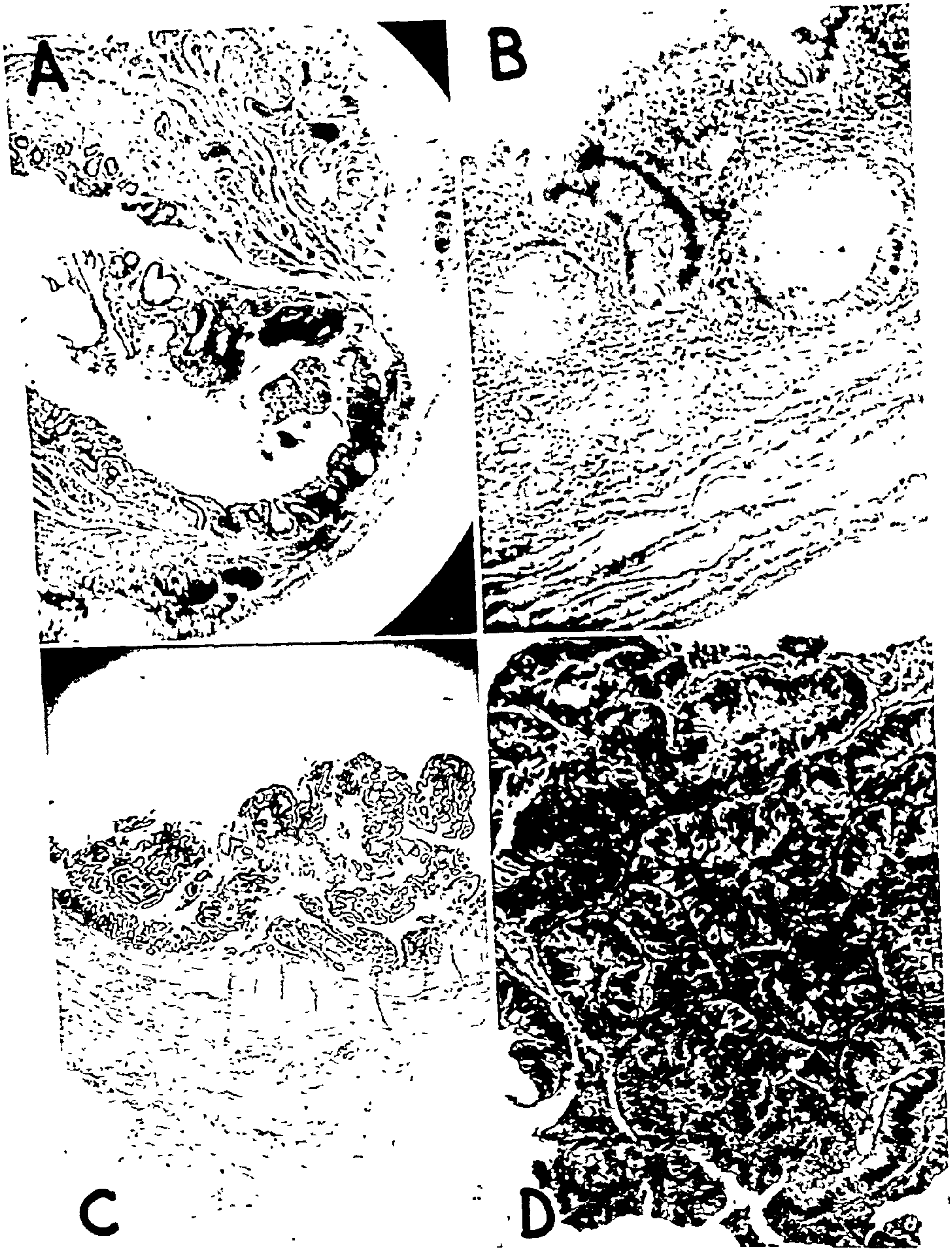

Fig. 1. *A*, low power photomicrograph of ureter showing lumen lined by glands resembling those seen in large bowel mucosa. *B*, high power photomicrograph of ureter showing glands lined by tall columnar cells and dense lymphocytic infiltration. *C*, low power photomicrograph through tumor in ureter showing its papillated structure and superficial growth. *D*, high power photomicrograph of tumor in ureter showing atypical gland formation.

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METAPLASIA OF URETERAL EPITHELIUM RESULTING IN INTESTINAL MUCOSA AND ADENOCARCINOMATOUS TRANSFORMATION: REPORT OF TWO CASES

NORMAN H. JACOB, JR. AND WALTER MAU

From the Department of Pathology, Veterans Administration Center, Wadsworth, Kansas

Since von Brunn's article in 1893, urologists and pathologists alike have been interested in epithelial abberancy in the urinary tract. Numerous writers, among them Aschoff, and Stoerk and Zuckerkandl, and in recent times Stirling and Ash, as well as other contemporary writers, have studied in detail the pathogenesis of so-called "epithelial nests or buds." There have been various schools of thought as to their origin, ranging from the original, almost unquestioned acceptance of von Brunn's thesis of downward proliferation and central degeneration of pinched off transitional cell nests to the present more generally accepted theory of epithelial proliferation and deepening of mucosal folds into underlying loose subepithelial tissue. As far as the bladder is concerned, the teaching that these cell nests can further change from transitional cells to squamous epithelium or mucin producing glands is rarely questioned by any of the recent authors.

Stoerk and Zuckerkandl probably first called attention to the malignant potentialities of cystitis glandularis. Patch and Rhea went further to predict that future histologic study would prove a definite relationship between cystitis glandularis and adenocarcinoma of the bladder. Hyperplasia and metaplasia of urinary epithelium is, therefore, of more than academic interest. Recent workers have focused much attention to this process, especially as it relates to proliferative tumors of the ureter. Everett and Wayburn have recorded a case which they believe demonstrates an early squamous cell carcinoma arising directly from epithelial buds in the ureter. Bothe has reported several surgical specimens of ureteral tumors, in all of which he could demonstrate epithelial nests in grossly normal portions of the ureter. It is the purpose of this paper to present very briefly the case histories of 2 patients treated in the Wadsworth Veterans Administration Hospital, in both of which epithelium of the intestinal type was found in the ureter, and in 1 case this condition was associated with adenocarcinoma.

CASE REPORTS

Case 1. A 36 year old white man was discharged from the Army in August 1943, after he was found to be suffering from renal calculi and chronic urinary infection. Six weeks later he was studied in this hospital. The original diagnosis was re-affirmed and a nephrectomy performed. Technical difficulties, incident to the dense fibrous adhesions, as well as the poor condition of the patient, precluded the removal of the ureter. After an uneventful recovery, he went home.

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through the tumor presented the typical picture of adenocarcinoma, and random sections in the renal pelvis revealed glands resembling those seen in the mucosa of the large bowel. The entire ureter and renal pelvis were thickened by mononuclear and round cell infiltration and connective tissue proliferation. Several sections through the tumor revealed it to be without deep extension or destruction of the ureteral wall (figs. 1, *C* and *D*, and 2).

DISCUSSION

There is no way of conclusively proving that the presence of intestinal-like epithelium in these 2 cases may not have been the result of embryological development. On the other hand, chronic inflammation is so pronounced a feature in both the clinical history and microscopic picture that possibly we must ascribe to it more than incidental significance. The bacterial, mechanical, and physical trauma to which the exstrophied bladder is submitted is well known. In all of 12 exstrophied bladders studied by Scholl, glands resembling those seen in the mucosa of the large bowel were encountered. We know of no substantial reason for not considering that mechanical irritation incident to the constant presence of a rough renal calculus or possibly that also irritating exudates could not stimulate the same response in the transitional epithelium of the ureter as is thought to occur in the bladder. We are inclined to believe that long standing chronic irritation may be a major factor in stimulating proliferation of transitional epithelium and downward penetration of mucosal folds in our 2 cases. The metaplasia which subsequently followed may or may not have been the result of chronic inflammation. Stirling and Ash believe that vitamin A deficiency may play at least some part in the metaplasia which results in squamous transformation. On the basis of experimental studies on the endometrium and tracheal epithelium of rats, McCullough and Dalldorf showed that metaplasia could be produced by feeding vitamin A deficient diets alone. Such changes could be precipitated prematurely by factors which stimulate increased growth rate of epithelium, such as mechanical and inflammatory irritation or hormonal stimulation.

Craig, and Patch and Rhea, and Stirling and Ash have ascribed definite malignant potentialities to glandular metaplasia in the bladder. Adenocarcinoma and cystitis glandularis have been seen side by side in the same bladder. The same also can be said of leukoplakia and squamous cell carcinoma of the bladder. Stoerk and Zuckerkandl were among the first who pointed out that epithelium which had acquired the habit of proliferation and had changed into epithelium of the mucin producing type might also be expected to play a role in the development of malignant neoplasms. In one of our cases intestinal type mucosa was encountered in one portion of the ureter with atypical cells and adenocarcinoma in another area. There was no evidence of adenocarcinoma in any other organ of the body. The neoplasm was only mucosal in depth without penetration into the underlying ureteral muscle.

It has been suggested that the epithelium of the ureter and bladder possesses different latent potentialities since very careful studies of significant numbers of

His urinary infection, however, persisted, but he did not again seek admission to this hospital until February 1947. At this time pain in the right flank, soreness in the right thigh, chills, fever, and generalized aching were his chief complaints. X-rays revealed a large calculus in the remaining ureteral stump. A right ureterectomy was performed.

The gross appearance of the ureter showed nothing unusual except a large calculus and a markedly thickened wall. Microscopic sections revealed mucosal crypts lined by tall columnar cells with basally placed nuclei and droplets of mucin in the cytoplasm. A well developed muscularis and lymph follicles were also noted. The entire ureteral wall was the seat of a dense round cell infiltration and proliferation of capillaries and dense fibrous connective tissue. The microscopic resemblance to appendiceal mucosa was striking (fig. 1, *A* and *B*).

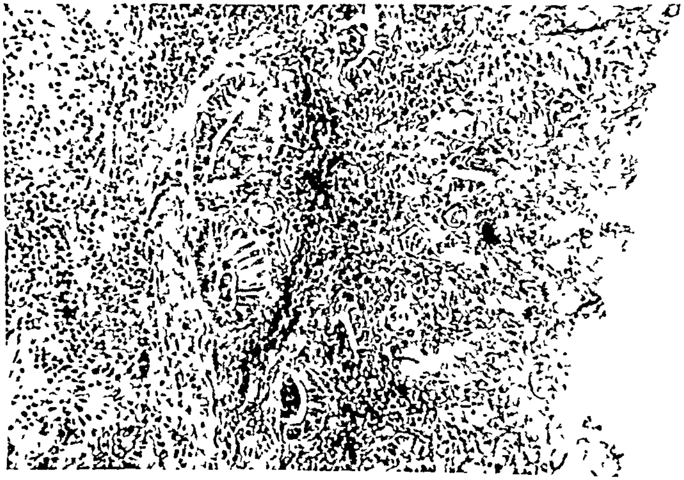

FIG. 2. High power photomicrograph of section from renal pelvis showing glands lined by tall columnar epithelium surrounded by dense lymphocytic infiltration.

Case 2. A 57 year old white man dated the onset of his present illness to 1945, at which time his left kidney was explored elsewhere. In September 1948, he was admitted to this hospital complaining of "gas pains and bloating." He was also suffering from pain in the left flank and the left lower quadrant. On physical examination a tender, left lower quadrant mass was found. X-ray examination revealed an irregular filling defect and distortion of the ureteropelvic junction on the left. The surgeons found a small, fibrotic, contracted kidney which was firmly bound bown by dense fibrous tissue. In the renal pelvis a large calculus could be palpated. A soft tissue mass occupied the lumen and enlarged the upper end of the ureter. The tumor, ureter, renal pelvis, and kidney were removed.

The walls of both the ureter and renal pelvis were thickened. At the ureteropelvic junction there was a papillary mass completely filling the lumen for a distance of 3 cm. Step sections were made 1 cm. apart along the entire length of the ureter, through the tumor, and into the renal pelvis. Much of the transitional epithelium was desquamated, but 1.5 cm. below the tumor, glands lined by tall columnar epithelium with basally placed nuclei were encountered. Sections through the tumor presented the typical picture of adenocarcinoma, and random sections in the renal pelvis revealed glands resembling those seen in the mucosa of the large bowel. The entire ureter and renal pelvis were thickened by mononuclear and round cell infiltration and connective tissue proliferation. Several sections through the tumor revealed it to be without deep extension or destruction of the ureteral wall (figs. 1, *C* and *D*, and 2).

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It has been suggested that the epithelium of the ureter and bladder possesses different latent potentialities since very careful studies of significant numbers of ureters in unselected autopsies have not revealed the presence of glandular structures with mucin producing properties. The findings in our cases would not tend to substantiate this assumption. Not only have these cells transformed into epithelium resembling intestinal mucosa but in 1 case they appear to have gone further and formed a neoplasm morphologically identical to those observed in the large intestine. So far as we are able to determine, this tumor is quite rare.

SUMMARY

Two cases of glandular metaplasia of the ureter resulting in epithelium resembling that seen in the large intestine are presented.

One case also showed a papillary adenocarcinoma similar to those observed arising in intestinal mucosa. This type of tumor of the ureter is very rare and we believe may arise in metaplastic glandular epithelium.

Chronic inflammation was a pronounced feature in both cases reported here.

The authors wish to express their gratitude to Dr. Ferdinand C. Helwig, consultant in pathology, Veterans Administration Center, Wadsworth, Kansas, for his help and guidance in the preparation of this manuscript.

REFERENCES

Aschoff Quoted by Morse
Bothe, A E J Urol , **53:** 451, 1945.
von Brunn Quoted by Morse
Craig, L G J Urol , **42:** 1197, 1939
Everett, H. S and Wayburn, G J J Urol , **56:** 310, 1946
Fagerstrom, D P J Urol , **59:** 333, 1948
McCullough, K and Dalldorf, G Arch Path , **24:** 486, 1937
Morse, H D Am. J Path , **4:** 33, 1928
Patch, F S and Rhea, L J Canadian Med Assoc J , **33:** 597, 1935
Scholl, A J Ann Surg , **75:** 365–371, 1922
Stirling, W C and Ash, J E South Med Journ , **34:** 358, 1941
Stirling, W C. and Ash, J E J Urol , **45:** 342, 1941
Stoerk, O and Zuckerkandl, O Ztschr f Urol , **1:** 133, 1907

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SURGICAL MANAGEMENT OF THE PAINFUL BLADDER

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We all have met, at one time or another, patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate often, at all moments of the day and of the night, and suffering pains every time they void. We all know how these miserable patients are unhappy, and how those distressing bladder symptoms get finally to influence their general state of health, physically at first, and mentally after a while. These patients, all chronic cases, can be classified into four categories.

First, we have those patients who have had unilateral renal tuberculosis, and who, after nephrectomy, contrary to the usual evolution, have continued to suffer from their bladder with night and day frequency and also pain on micturition, and this, despite all postoperative treatments. We also have in this category those cases of bilateral renal tuberculosis with a very slow evolution and in which, no treatment whatsoever has given any beneficial results.

Secondly, another group of patients are embarrassed by those same symptoms due to Hunner cystitis or interstitial cystitis for which, actually all treatments have given very poor results in most cases.

Thirdly, is the group of those patients suffering from chronic cystitis due to common infection, and who have a contracted bladder due to the sclerosing process following frequent acute infections, or on whom, the bladder sclerosis has been provoked by therapeutic accidents by the use of antiseptics which were too strong.

Fourthly, we have those patients who have inoperable cancer of the bladder and who suffer tremendously.

On all these patients, the two symptoms which dominate the whole clinical picture and which are among the most distressing ones, are first, the frequency which is a frequency of all moments, day and night, not influenced by either rest of movement and which is relieved by no medication whatsoever; and, secondly, the pain which is intolerable whether it is felt as a sensation of fullness in the hypogastric region, as in the case of a contracted bladder which does not tolerate more than fifty to a hundred cubic centimeters of urine, without provoking this intolerable sensation obliging the patient to void every half hour or every hour, day and night, without any relief; or, the other kind of pain which is the pain suffered at micturition and felt as disagreeable burning sensation at the end of urination when the bladder is empty.

Up to now, those patients have had very little relief by all treatments usually prescribed, whether they are local i.e. bladder irrigations, bladder instillations, fulgurations of ulcers, bladder distention, etc., or general treatment. In the cases

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Read at annual meeting, Northeastern Section, American Urological Association, September 8, 1949.

where there is infection, the general use of sulfa drugs, antibiotics, mostly penicillin and streptomycin, and, more lately, aureomycin, has given a certain degree of relief but not a complete one. In other cases, where all treatments were unsuccessful, we were often forced to divert the urinary stream either by a cutaneous ureterostomy or by a ureterosigmoidostomy, two operations which give excellent results when well performed, but which are in no way, a solution to the problem.

What can we do for those patients?

Here is the problem we want to study in this short paper.

We think that the solution lies in the surgical action that can be taken towards the innervation of the bladder and this being so, we will study this innervation briefly to know where and how to act.

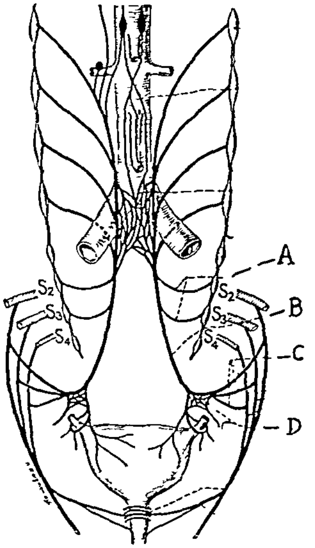

FIG. 1. Schematic innervation of the bladder (Ginestié)

ANATOMY OF BLADDER NERVES

The bladder innervation can be divided into three parts: we have the sensory innervation, the motor innervation and, finally, the autonomous intramural innervation, independent of the two preceding ones.

In this short paper, it is impossible to describe in detail the innervation of the bladder, but the main point will be reviewed briefly.

The bladder draws its innervation from two nervous masses known as the hypogastric ganglions which are situated in the sacral cavity on both sides of the rectum, practically down under the vesico-ureteral junction. These ganglions receive some pregnaglionic fibers and give off postganglionic fibers which constitute the bladder nerves (fig. 1).

The preganglionic fibers are formed by three groups of nerve fibers.

First are the pelvic splanchnic nerves which constitute a double nervous plexus known as the hypogastric nerves, right and left, coming together on the median line to form the interiliac plexus described by Delmas and Laus and also known as the presacral nerves of Latarget. These nerves continue and individualize themselves again before entering the inferior mesenteric plexus or ganglion, lying on the anterior portion of the aorta. The convergence of those fibers in a fixed anatomical point greatly facilitates a surgical action on them, such as the presacral neurectomy.

Secondly are the fibers of the lateral sacral nerves, of sympathic origin, which are two or three in number and come from the second and the third sacral ganglions, to unite on the posterior part of the hypogastric nerves in their high portion.

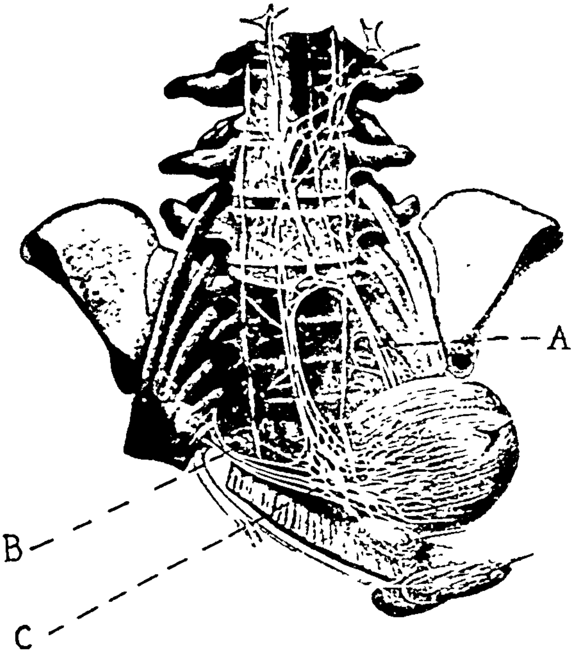

FIG. 2. Bladder innervation (Muller)

Thirdly are the erector nerves which are two or three in number and come from the pudic plexus.

It is important to note that the preganglionic branches carry mostly two nerous influxes: the superior one, from the splanchnic, originating in the sympathic and the inferior one, that is the erector nerves, which originate from the parasympathic; these two groups unite and form the hypogastric ganglion which gives off postganglionic fibers innervating the bladder.

So, we see that the bladder nerves, as studied by Latarget and Rochet are constituted by postganglionic fibers coming from the hypogastric ganglions. There are also a few independent fibers coming from the erector nerves not going through the ganglions. All of those postganglionic nerves terminate in the bladder wall itself by three kinds of nervous fibers: the motor fibers, the vascular fibers and the sensory fibers.

There exist also, in the bladder wall, a great number of ganglions which, by their formation, constitute true reflex centers that can play the part of an automatic vesical apparatus, when the normal nervous influxes of the bladder have been intercepted by a section. At no time, incontinence is observed, this being due to the automatism of this neurovegetative system.

In résumé, the bladder innervation depends on two great nervous influxes: one superior, sympathetic, coming through the hypogastric nerves from the interiliac plexus or presacral nerves and also the latero-sacral chain; and the other one, inferior, parasympathetic, coming from the erector nerves.

As we have just seen, these two nervous influxes are at one time condensed in such a point that it is possible to perform a surgical act, fairly precise and elective on one or the other; but we have to bear in mind that there are also a few fibers which are not in this plexus and which, on account of this fact, can not be acted upon precisely and this may at times alter the expected results (fig. 2).

PHYSIOLOGY OF BLADDER NERVES

We will now study briefly the role of these nerves.

Vesical sensitivity. It is assured by two influxes, one main influx which comes from the erector nerves which constitute the sensory part of the reflex arc for micturition, the normal sensation of fullness and voiding and the painful sensations. Richer has proven that sectioning the erector nerves which are also the only nerves blocked by epidural or parasacral anesthesia, cuts off all the sensations coming from the bladder. There is also the presacral nerve influx which carry the sensations from the vesical peritoneum and may be the ones from the bladder neck, this point being still not cleared up, definitely; we have to mention also, another important route of the vesical influx, independent of the ones we have just described because it is not a part of the bladder innervation itself, and comes from the internal pudic nerve which assures the sensitivity of the posterior urethra.

Vesical function. Vesical function is carried through three routes, the erector nerves carrying the influx to the detrusor; the postganglionic fibers of the lateral sacral sympathetic chain carrying the influx to the internal sphincter; and the internal pudic nerve carrying the influx to the external sphincter of the bladder. The vesical function has also to be studied under three aspects: the filling of the bladder, its normal retention of urine and, micturition. The filling of the bladder is assured by the detrusor and by its particular tonus which is in relation with volume and pressure. The normal retention of urine is due to a difference between the tonicity of the neck of the bladder and the detrusor. The micturition is a complex act in which a series of reflexes are taking place, first, to start the urination and, secondly, to assure its normal fulfilment. The normal micturition has to be conscious, voluntary, complete and painless. It is a result of a real teamwork between the detrusor and the sphincteric system explaining how we can observe normal micturition, reflex micturition, and automatic micturition which we get after denervation of the bladder.

All these physiological data have been described by many authors, but the principal contemporary surgeons who have done the most precise work on this problem are Richer, from Lyon, and Ginestie, from Montpellier.

Knowing now the origin and the pathways of the nervous influxes to and from the bladder, we can decide which action to take if we want to relieve, first, the pain, and then the frequency which is, in some degree, in relation with the pain or, at least, this disagreeable sensation of bladder fullness or distention, because all sensations having disappeared from the bladder, this reservoir will bear more distention and so, increases its capacity.

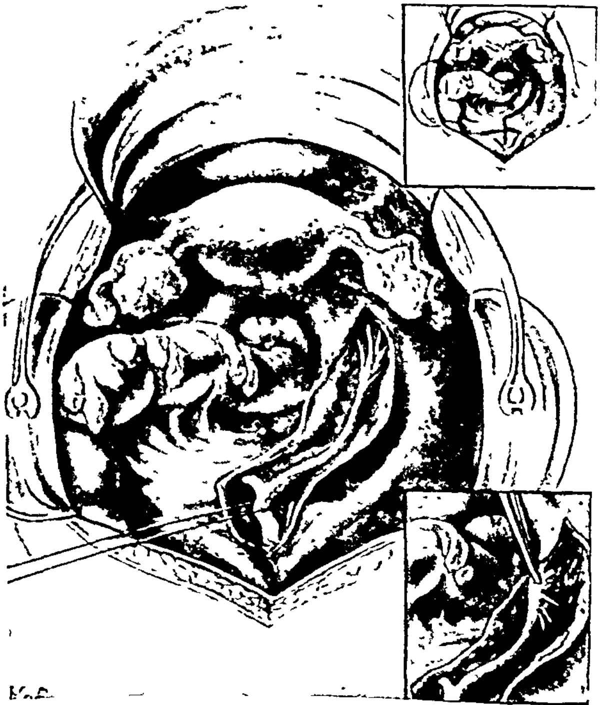

Fig. 3. Surgical exposure of presacral, hypogastric and erector nerves; also of hypogastric ganglion.

To reach the expected results, the surgical act will have to consist in a section of the hypogastric nerves, of the erector nerves and the removal of this part of the hypogastric ganglion where the hypogastric and the erector nerves enter the nervous mass, in order to section all sympathetic fibers of sacral origins that enter the hypogastric nerve in its lowest portion and thus have a complete operation.

A consequence of the operation which should by all means be explained to the patient is that the sexual sensations will be greatly modified if not altogether abolished.

TECHNIQUE OF OPERATION

There are many routes that can be used: a transperitoneal route, a retroperitoneal route and, finally, a sacral route. We have been using the less complicated one which is, in our opinion, the transperitoneal route.

The technique in itself is very easy (fig. 3). First, a low suprapubic median incision is made and the anterior peritoneum opened, bringing the setting to a good exposure of the region of the presacral nerves as in presacral neurectomy. Then, an incision of the posterior peritoneum is made on the body of the fifth lumbar vertebra to localize the presacral nerve. This being done, we can see this nerve dividing into two branches which are the hypogastric nerves, one right and one left. The presacral nerve is sectioned and then, the right hypogastric nerve is dissected straight down to the sacral cavity, opening up the peritoneum as need be for the exposure, in the direction of the point where the ureter enters the bladder; at that point, although it is very deep, we can see fairly easily, if there is not too much bleeding, the hypogastric ganglion and two or three branches of the erector nerves that come from behind to join it. This is where we section those erector nerves, between two ligatures, and also section the hypogastric ganglion and remove it with the whole of the hypogastric nerve (fig. 4).

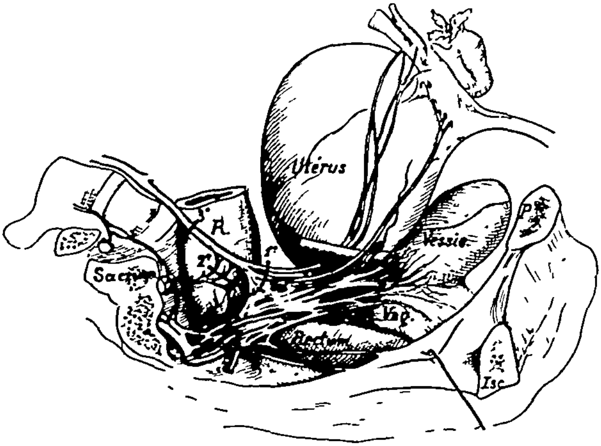

FIG. 4. Schematic illustration of sections to be performed

The operation is much more complicated on the left side because the left hypogastric nerve passes under the mesosigmoid. So, in order to avoid traumatizing the vessels of this part of the bowels, what we have been doing is as follows: After dissecting the left hypogastric nerve to the mesosigmoid, we apply a little traction on it in order to see its direction on the left side of the sigmoid and then, a second incision is made where the peritoneum retracts under the effect of the traction; the same procedure is then performed as on the right side.

Usually, there is very little bleeding if the dissection is carried smoothly, without too much trauma. At times, it is necessary to leave either thrombin, oxycel or gelfoam or some other coagulants before closing the posterior peritoneum. The anterior peritoneum is then closed without drainage and the abdominal incision is repaired adequately.

RESULTS

If the operation has been performed completely, first, the patient does not feel any more pain, and that is the main point. Secondly, the bladder fullness sensation is altogether different; it is felt as a sensation of internal pressure in the lower abdomen. Thirdly, we have observed no incontinence and no retention of urine, but we have to bear in mind that the micturition now taking place is, in no way, a reflex micturition as in paraplegic patients, because all the pathways of the reflex arcs have been interrupted. The main factor of urination now, is the automatism of the intramural neurovegetative system, and the accessory factors are the voluntary contractions of the abdominal muscles, with or without the help of outside pressure, and also the contractions of the perineal muscles; at first, it is mostly dribbling and later, it is a real micturition. Fourth, due to the absence of painful sensations, the bladder stretches, its capacity increases and the frequency gradually decreases. Fifth, the sexual impulses are abolished in most cases.

Although all of these facts generally take place after the operation, we think that, in some instances, where there is an abnormal distribution of the pelvic nerves as is sometimes observed on dissection, some nervous fibers may remain untouched and thus alter the results in one way or another.

On first thought, we may think that the facts observed here have a great similarity with the ones observed after the resection and the removal of the rectum for cancer; but we have to bear in mind that, even if those same nerves are partially or totally severed during the rectal operation, most of the bladder troubles encountered then are due to the falling of the bladder in a new cavity and also to the formation of a large area of scar tissue caused by the elaborate dissection of the rectum from the posterior wall of the bladder in which case, nearly all of the posterior wall of the bladder is frozen and can not contract. This does not happen in the operation just described.

Here are now, classified as to time, the observations made on our patients:—

Immediately after the operation: a) no bladder sensations, pain or fullness were felt, b) urination was mostly dribbling, which took place now and then, resembling stress incontinence or overflow incontinence. This lasted for a period of approximately 4 to 8 days during which period an indwelling catheter was left in place. After this period, the sensation of bladder fullness could be appreciated by the patient and he could urinate by contracting or pressing on the lower abdominal wall and also by contracting his perineal muscles to help empty the bladder.

At discharge time, that is on or about the fifteenth day after the operation, all of our patients felt no pain whatsoever on urination and they were urinating at regular intervals of from 1 to 2 or 3 hours, quantities varying between 100 to 250 cc, depending on the bladder capacity before the operation; this last fact being in direct relation with the state of the bladder before the operation.

After one to three months after the operation and in the late follow-up which, except for the last case, is of over one year, none had pain and all had complete urinary control with no incontinence and no residual urine and led normal lives.

We do not claim by any means, the honor of having been the originator of this operation, because we think that most of the credit goes to Richer who, in 1929, was the first surgeon to attempt the erector neurectomy to alleviate bladder pains.

PRESENTATION OF OUR CASES

Table 1 lists the cases that we have treated by this method.

Five patients on whom the operation was complete were all relieved definitely. Two patients on whom the operation was incomplete were partially relieved when only unilateral hypogastric and erector neurectomy were performed. One patient had no relief because the operation was incomplete, i.e. no erector neurectomy.

All these patients have been operated on, in the past 3 years, the first one on December 12, 1946, and the last one on February 22, 1949, and the follow up has been done on every one of them up to now.

In this series, a few interesting facts were observed.

Cases 4 and 6, one a case of Hunner cystitis and the other a case of chronic cystitis with leukoplakia, underwent cystoscopy before they left the hospital; in both instances, the examination showed normal bladders except for slight congestion of the neck of the bladder.

The other cases refused the cystoscopic examination. In case 7, tuberculosis of the bladder associated with pyuria and hematuria, the urine was clearing up at the time of the discharge and since, the patient has never had any recurrence of the hematuria but still has a few pus cells in his urine. This is due, we think, to the resting of the bladder.

All these patients had had previously all possible treatments this side of diversion of the urine, without any results; as we can see, now, this operation, when done completely, that is the presacral neurectomy with bilateral hypogastric neurectomy and bilateral erector neurectomy, gives encouraging results. The only drawbacks to the operation is that, in some cases, it is impossible, without too much risk, because of operative difficulties such as adhesions and bleeding, to do a complete operation, and that, in most of them, the sexual sensations are abolished.

Among these cases, some patients had been operated on before and there were so many adhesions that it was too risky to do a complete operation and we were reduced to do what could possibly be done. We think, though, that in those cases, where extensive adhesions are to be expected, the extraperitoneal route should be taken to do the section of the erector nerves and the resection of the hypogastric ganglions; but, we think that in most cases, the presacral neurectomy itself, can be done by the transperitoneal route, and so, combining the two techniques. The approach for the extraperitoneal route is the same as for the juxtavesical ureter. We have no experience with the sacral route which at times should be applied when indicated.

Unfortunately, there are patients who cannot be operated on for many reasons. For them, the problem can be undertaken by another method which is the infiltration of the hypogastric ganglions.

There are a few techniques by which this procedure can be done, some using the perineal route, others, the sacral route. We have been using this last one and here below is the technique followed, as described by Darget and Chenilleau:—

"The patient is placed in a knee-chest position; the dorsal spine of the fifth

TABLE 1

CASES	SEX	AGE	DIAGNOSIS	TREATMENT	RESULTS
1 Dec. 12/46	Female	35	Chronic cystitis and leukoplakia Contracted bladder	Presacral neurectomy and bilateral hypogastric neurectomy Unilateral erector neurectomy	Partial relief
2 Feb. 2/47	Female	62	Hunner cystitis	Presacral neurectomy and unilateral hypogastric neurectomy	No relief
3 May 5/47	Female	38	Chronic cystitis and leukoplakia Contracted bladder	Presacral neurectomy and bilateral hypogastric neurectomy Bilateral erector neurectomy	Complete relief
4 Feb. 3/48	Female	42	Hunner cystitis	Presacral neurectomy and bilateral hypogastric neurectomy Bilateral erector neurectomy	Complete relief
5 Apr. 15/48	Female	40	Tuberculosis	Presacral neurectomy and bilateral hypogastric neurectomy Bilateral erector neurectomy	Complete relief
6 May 28/48	Female	51	Chronic cystitis and leukoplakia Contracted bladder	Presacral neurectomy and bilateral hypogastric neurectomy Bilateral erector neurectomy	Complete relief
7 Nov. 4/48	Male	34	Tuberculosis	Presacral neurectomy and bilateral hypogastric neurectomy Bilateral erector neurectomy	Complete relief
8 Feb. 22/49	Female	66	Hunner cystitis	Presacral neurectomy and unilateral hypogastric neurectomy Unilateral erector neurectomy	Partial relief

lumbar vertebra is identified, then the sacral tubercles at the point of the sacrococcygeal junction and, finally, the tip of the coccyx. A perpendicular line is drawn on the line joining the apex of the coccyx with the sacral tubercle and on this perpendicular line, 4 cm. from the sacral tubercle, a spinal trocar is inserted. The trocar is then directed obliquely, in the direction of the dorsal spine of the fifth lumbar vertebra and, on penetration, it should slightly graze the sacral edge. The trocar goes through the sacro-iliac ligament which is felt, and is then pushed 1 to 2 cm. further. The tip of the trocar is then exactly in the intimate vicinity of the hypogastric ganglions where the hypogastric and erector nerves enter it; then, 20 cc of 1 per cent novocaine are injected while the trocar is being pulled back slowly for 1 to 2 cm. The same procedure is done on the other side."

The technique is precise and if need be, after having done the test with novocaine, we can use 20 cc of 95 per cent alcohol to produce a much longer action. This infiltration technique can also be used as a preoperative test; it is benign, it has no ill effects, it is easy to perform and it will give information as to what can be expected from the operation.

CONCLUSIONS

First, we know that the bladder innervation is disposed in such a way that it is possible *to act directly on a fixed point to relieve pain and frequency.*

Secondly, we believe that all those patients with bladder trouble, who are not relieved by any treatments, should be operated on; the operation in itself is without any danger and, even if the results are not perfect, the patients can not be any worse afterwards than they were previously and we think that this point only, is enough to justify the operation.

Thirdly, in those cases where the patient is a bad risk, we, at least, should try the infiltration method.

REFERENCES

Barrington, J. B.: Localization of the paths of micturition in the spinal cord of the cat. Brain, 56: 148, 1933.

Beattie and Kerr: Effects of diencephalic stimulation on urinary bladder tonus. Brain, 59: 302, 1936.

Cheetham, J. G.: Presacral neurectomy for relief of certain types of bladder dysfunction and pain. J. Urol., 37: 148, 1937.

Darget, R.: Treatment of inveterate cystitis. J. Int. Coll. Surg., 11: 49, 1948.

Denny-Brown and Robertson: Physiology of micturition. Brain, 56: 188, 1933.

Douglas, H. L.: Excision of the superior hypogastric plexus in the treatment of intractable interstitial cystitis. Am. J. Surg., 25: 249, 1934.

Ecker and Laurie: Bladder control: Brief review. J. Urol., 45: 397, 1941.

Elliott, T. R.: The innervation of the bladder and urethra. J. Phys., 35: 367, 1906–07.

Ginestie, J.: Innervation sensitivo-motrice de la vessie. J. d'urol., 46: 497, 1938.

Goethals-Borin, J.: Opération de Richer pour cystite par tuberculose rénale bilatérale. Presse méd., 50: 725, 1942.

Jacobson, Braasch and Love: Presacral neurectomy for intractable vesical pain and neurogenic vesical dysfunction. Surg. Gynec. and Obst., 79: 21, 1944.

Langworthy, Reeves and Tauber: Autonomic control of the urinary bladder. Brain, 57: 266, 1934.

Langworthy, Lewis and Dees: Behavior of the human bladder freed from cerebral control. J. Urol., 36: 576, 1936.

Latarget and Bonnet: Plexus hypogastrique chez l'homme. Lyon chir., 9: 619, 1913.

Latarget and Rochet: Plexus hypogastrique chez la femme. Gyn. and Obst., 6: 225, 1922.

Learmonth, J. R.: Neurosurgery in diseases of the urinary bladder. Am. J. Surg., 16: 270, 1932.

Leichtenstern (Vienne): Wiener klin. Wochenschr., 33: 1248, 1912, Trans. by Lumiere, A.: Innervation centrale de la vessie. J. d'urol., 2: 595, 1912.

Nesbit, R. M. and McLellan: Sympathectomy for the relief of vesical spasm and pain resulting from intractable bladder infection. Surg. Gynec. and Obst., 57: 741, 1947.

PEARL, F. L. AND STRAUSS, B.: Presacral neurectomy and sacral ganglionectomy in affections of the bladder. J. Urol., 39: 645, 1938.
RICHER, V.: Traitement des cystites tuberculeuses rebelles et des cystalgies néoplasiques par la section des nerfs erecteurs. J. d'urol., 39: 60, 1935.
RICHER, V.: Enervation vésicale. Presse méd., 40: 1580, 1932.
RICHER, V. AND GINESTIE, J.: Chirurgie du systéme nerveux vésical. Presse méd., 62: 742, 1948.
ROCHET AND LATARGET: Etude sur les voies d'abord chirurgical du plexus hypogastrique et de son ganglion. Lyon chir., 10: 549, 1913.
ROCHET: Traitement chirurgical des cystites douloureuses. Lyon chir., 18: 462, 1921.
ROSE, D. K.: Physiology of the bladder. J. Urol., 43: 190, 1940.
SENGEN AND ROTHFELD: On sensation of the bladder. Urol. and Cut. Rev., 51: 454, 1947.
WERTHEIMER AND MICHON: Névrotomie du nerf honteux interne. J. Chir., 31: 497, 1928.
ZIMMERMAN, L. J.: The neuromuscular physiology of the detrusor muscle of the urinary bladder. J. Urol., 40: 766, 1938.

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STATISTICAL AND ANALYTIC REVIEW OF THE FINAL RESULTS OF TRANSURETHRAL RESECTION FOR CORD BLADDER

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In previous communications from the Mayo Clinic[1–4] it has been shown that in many cases neurogenic vesical dysfunction (in the chronic stage) may be successfully treated by transurethral resection of the vesical neck. Articles have also appeared from other urologic centers describing successful results with this operation.[5–9] The most disconcerting aspect of this type of treatment, however, has been the difficulty of making an intelligent selection of patients for operation. Experience has shown that in many cases almost miraculous results are obtained, whereas in others the results have been disappointing. To date we have been unable to predict with reasonable accuracy which patients might be expected to respond favorably to operation. It is with this problem in mind that this study was undertaken. We were interested in finding out the percentage of patients who have been helped and in learning, if possible, any factors which might aid in selection of patients for operative treatment.

There are certain types of neurogenic vesical dysfunction which are not

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[1] Emmett, J. L.: Transurethral resection in treatment of true and pseudo cord bladder. J. Urol., 53: 545–564, 1945.

[2] Emmett, J. L.: Further observations in the management of cord bladder by transurethral resection. J. Urol., 57: 29–41, 1947.

[3] Emmett, J. L. and Bisquertt, J. E.: Transurethral resection in the treatment of vesical dysfunction secondary to inflammatory, degenerative and traumatic lesions of the spinal cord. S. Clin. North America, 27: 950–977, 1947.

[4] Emmett, J. L. and Dunn, J. H.: Transurethral resection in the surgical management of cord bladder. Surg., Gynec. & Obst., 83: 597–612, 1946.

[5] Baker, W. J., Carney, J. and DeRosa, F.: Transurethral resection for relief of urinary retention in patients with neurologic lesions. J. Urol., 63: 300–318, 1950

[6] Bumpus, H. C., Jr., Nourse, M. H. and Thompson, G. J.: Urologic complications in injury of the spinal cord. J. A. M. A., 133: 366–368, 1947.

[7] Dees, J. E.: Transurethral resection for neurological bladder. J. Urol., 60: 907–914, 1948.

[8] Thompson, G. J.: Cord bladder; restoration of function by transurethral operation. U. S. Nav. M. Bull., 45: 207–214, 1945.

[9] Thompson, G. J., Nourse M. H. and Bumpus H. C., Jr.: Treatment of the paraplegic: Observations in a series of 101 cases. J. Urol., 57: 1085–1096, 1947.

included in this study because we believe that they have been adequately studied and evaluated previously. These include neurogenic vesical dysfunction resulting from 1) tabes dorsalis, 2) diabetic tabes, 3) surgical removal of the rectum and sigmoid and 4) myelodysplasia (spina bifida) found in infants and children. In two previous reports from the Mayo Clinic on the subject of cord bladder associated with tabes dorsalis[10, 11] it was shown that almost 90 per cent of such patients obtained good results following transurethral resection (a total of 79 patients were included in these reports). A very similar condition occurs in patients with severe, long-standing diabetes associated with diabetic neuropathy (diabetic neuritis). Equally good results were obtained in these patients, although the total number of patients treated has been relatively small.[12] Vesical dysfunction following surgical removal of the rectum and sigmoid has formed the basis of two previous communications concerning 57 patients[13, 14] who were treated by transurethral resection. Almost 90 per cent of good results were obtained in this group of patients. It is our opinion, therefore, that the results of treatment of patients falling in these three groups are sufficiently good that no selection of patients is required for operation and that for all practical purposes a therapeutic problem ceases to exist in these cases.

Such a favorable report may not be made, however, on the fourth group of patients; namely, infants and children suffering with myelodysplasia. Results in these cases have been disappointing. Of 18 such patients treated by transurethral resection, good results were secured in only a third (6 patients). The reason for the lower incidence of good results in these cases has been fully discussed elsewhere.[15]

MATERIAL FOR STUDY

This communication concerns 143 patients with neurogenic vesical dysfunction who underwent transurethral resection at the Mayo Clinic prior to January 1, 1949. As stated previously, it *does not include* patients with tabes dorsalis, diabetic tabes or surgical removal of the rectum and sigmoid, or infants and children with myelodysplasia. It *does include* patients with *transverse lesions* of the spinal cord resulting from any type of lesion, such as traumatic, inflammatory, neoplastic, postoperative (such as operations on the spinal cord for tumor, protruded intervertebral disk, and so forth) or the result of spinal anesthesia. It also includes a small group of patients with *miscellaneous lesions*. Almost half of these

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[10] Emmett, J. L. and Beare, J. B.: Bladder difficulties of tabetic patients; with special reference to treatment by transurethral resection. J. A. M. A., 117: 1930–1934, 1941.

[11] Emmett, J. L. and Beare, J. B.: Transurethral resection for vesical dysfunction in cases of tabes dorsalis. J. A. M. A., 136: 1093–1096, 1948.

[12] Emmett, J. L., Daut, R. V. and Sprague, R. G.: Transurethral resection for neurogenic vesical dysfunction in cases of diabetic neuropathy. J. Urol., 61: 244–257, 1949.

[13] Bisquertt, T. J. E. and Emmett, J. L.: Transurethral resection to relieve urinary retention following operations on the rectum and sigmoid. J. Urol., 57: 771–778, 1947.

[14] Emmett, J. L. and Cristol, D. S.: Urinary retention following surgical operation on the rectum and sigmoid. J. A. M. A., 126: 1077–1079, 1944.

[15] Emmett, J. L. and Helmholz, H. F.: Transurethral resection of the vesical neck in infants and children. J. Urol., 60: 463–478, 1948.

latter patients were afflicted with multiple sclerosis, whereas the remainder had a variety of lesions, such as combined sclerosis, degenerative lesions of the cord, arachnoiditis, amyotrophic lateral sclerosis and Parkinson's disease. All of the patients in the foregoing categories who have undergone transurethral resection at the clinic before January 1949, have been included in this study. There was a *total of 143 cases* found which could qualify for this study. Of the 143 cases, 114 were the result of transverse lesions of the cord, whereas 29 were miscellaneous lesions.

OBJECT OF STUDY

The object of this study was 1) to try to determine the percentage of patients with neurogenic vesical dysfunction who were being helped by transurethral operation; and 2) to determine, if possible, preoperative characteristic factors or classifications of patients which might help in predicting the outcome of treatment. The net result of such findings, we felt, should help considerably in the selection of patients for operation. It seemed to us important that whenever possible a comparison of immediate and late results be made. To this end we sent letters of inquiry to all of the patients who had undergone operation prior to 1948. A summary of the information received is included in this paper.

THEORETICAL CONSIDERATIONS

Since the theoretical considerations of the reason for transurethral resection in cases of neurogenic vesical dysfunction have been fully discussed in previous papers,[1–4] they will not be repeated here. It should be emphasized that we have been primarily concerned with the chronic phase of the disease; namely, after the usual methods of treatment (subrapubic and urethral catheter drainage, tidal and intermittent drainage and re-education) have been tried for a sufficient time (many months or years) to demonstrate that further spontaneous improvement was unlikely to occur. With increasing experience we have come to the conclusion that the disturbance of the urinary sphincters is probably the greatest single factor in neurogenic vesical dysfunction[15-18] and it is toward this disturbed mechanism that treatment should be directed.

ANALYSIS OF DATA ON THE 143 CASES SELECTED FOR THIS STUDY

Follow-up data.—Of the 143 cases presented in this study, in 20, operation was performed prior to 1944. In the remainder of the cases operation was performed as follows: 1944 and 1945, 44 cases; 1946, 30 cases; 1947, 28 cases, and 1948, 21 cases. In an effort to compare immediate and late results, letters of inquiry were sent to the 122 patients who underwent operation prior to 1948. The response to the follow-up is summarized in table 1. It will be noticed that

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[16] Emmett, J. L. Daut, R. V. and Dunn, J. H.: Role of the external urethral sphincter in the normal bladder and cord bladder. J. Urol., 59: 439–454, 1948.

[17] Head, H. and Riddoch, G.: The automatic bladder, excessive sweating and some other reflex conditions, in gross injuries of the spinal cord. Brain., 40: 188–264, 1917.

[18] Shelden, C. H. and Bors, E.: Subarachnoid alcohol block in paraplegia; its beneficial effect on mass reflexes and bladder dysfunction. J. Neurosurg., 5: 385–391, 1948.

follow-up data were obtained for 98, or approximately 80 per cent, of the 122 cases in which operation was done prior to 1948. If the 21 cases in which operation was done in 1948 (and in which sufficient time had not elapsed at this writing to obtain a follow-up study) are included, it can be stated that follow-up data were available in approximately 69 per cent of the total 143 cases used in this study.

Age and sex.—An analysis of the cases from the standpoint of age and sex is given in table 2. As might be expected, the great majority of patients were male; namely, 125 male and 18 female. It will also be noticed from this table that the preponderance of transverse lesions occurred in the 21-year through 60-year age group as compared with 41 through 70 years for the group of miscellaneous lesions.

TABLE 1. *Completeness of follow-up study**

DATE	TOTAL CASES	NO FOLLOW-UP	3 TO 12 MONTHS (NOT INCLUDING 12 MONTHS)	1 TO 2 YEARS	2 TO 3 YEARS	3 YEARS OR MORE
Before 1944	20	6	2	1	1	10
1944 and 1945	44	7	0	2	0	35
1946	30	8	0	0	0	22
1947	28	3	0	3	22	0
Total	122	24	2	6	23	67

* The 21 cases in 1948 are not included in this table, as sufficient time has not elapsed for follow-up.

TABLE 2. *Age and sex correlated with type and completeness of lesion*

AGE, YEARS	INCOMPLETE TRANSVERSE LESIONS			COMPLETE TRANSVERSE LESIONS			MISCELLANEOUS			TOTAL
	Total	Male	Female	Total	Male	Female	Total	Male	Female	
11–20	7	5	2	6	6	0	0	0	0	13
21–30	12	11	1	9	5	4	0	0	0	21
31–40	15	13	2	11	9	2	3	2	1	29
41–50	20	19	1	8	8	0	12	9	3	40
51–60	17	17	0	1	1	0	8	6	2	26
61–70	7	7	0	0	0	0	5	5	0	12
71–80	1	1	0	0	0	0	1	1	0	2
Total	79	73	6	35	29	6	29	23	6	143

Etiology of neurologic lesions.—Of the 143 cases studied, 114 were the result of transverse lesions of the spinal cord and 29 were classed as miscellaneous lesions. The etiologic agents in the 114 transverse lesions were as follows: traumatic 64; inflammatory 23; postoperative removal of spinal cord tumor or protruded intervertebral disk 20; after spinal anesthesia 7. The etiologic agents in the 29 miscellaneous lesions were as follows: multiple sclerosis 14; combined sclerosis 5; degenerative lesions of the spinal cord 5; arachnoiditis 3; amyotrophic lateral sclerosis 1, and Parkinson's disease 1.

Completeness of transverse lesions: Definition of terms.—It became apparent early in the study of the 114 cases with transverse lesions of the spinal cord that from the standpoint of preoperative analysis, as well as results, the cases fell into two distinct groups which we have labeled 1) incomplete (ambulatory) and 2) complete (nonambulatory). Although it may be difficult to make a hard and fast rule concerning such a division of patients, from a working standpoint the distinction is easily made. In the group of *incomplete lesions* were placed those patients whose original lesion may not have resulted in complete paralysis or those whose original lesion had caused complete paralysis but whose subsequent recovery had allowed them partial use of the paralyzed extremities. For the most part these were the patients who could hobble around with crutches and canes, with a varying degree of spastic, shuffling gait. In the group of *complete lesions* were placed those in whom the paralysis below the lesion was complete and no recovery had occurred. These patients are ordinarily called bed patients, a term which is no longer applicable, as many have been taught to move themselves about by the use of their arms and shoulders and with various types of swinging gaits with crutches and other walking aids. In this group of 114 transverse lesions, 35 were regarded as complete and 79 as incomplete.

TABLE 3. *Etiology of 114 transverse lesions correlated with completeness of the lesions*

ETIOLOGY	TOTAL	COMPLETE	INCOMPLETE
Traumatic	64	24	40
Inflammatory	23	7	16
Postoperative cord tumor or disk	20	4	16
After spinal anesthesia	7	0	7
Total	114	35	79

In tables 3 and 4 an attempt has been made to correlate the etiology and level of the transverse lesions with the completeness of the lesion. It is interesting to note (table 3) that practically all of the lesions resulting from spinal anesthesia or operations on the spinal cord for tumor and disk were incomplete lesions. Regarding the level of the lesion, it is apparent (table 4) that the lower the level of the lesion, the greater is the chance of the lesion being incomplete or of subsequent partial recovery to an "incomplete" stage. As would be expected in a group composed primarily of civilian patients, the lesion in 68 per cent of these 114 cases was located at T12 or below; 85 per cent of the 79 incomplete lesions were located at T12 or below; whereas only 31 per cent of the 35 complete lesions were at this level.

Duration of the cord lesion.—As was mentioned in the beginning of this paper, our work has been primarily directed toward the chronic stage of this disease. In the great majority of cases the standard methods of conservative treatment have been given a trial before the patients were seen by us, so that the chronic pattern of the vesical dysfunction has been established. These data appear in table 5, in which it can be seen that in approximately 75 per cent of the patients with transverse lesions more than a year had elapsed between the time of onset of the neurologic lesion and transurethral resection of the vesical neck.

TABLE 4. *Transverse lesions (114 cases). Level of lesion: complete and incomplete*

LESION	CASES	LEVEL OF LESION			
		Widespread or indefinite	Cervical	Thoracic	T12 and below
Incomplete	79	1	2	9	67 (85 per cent of 79)
Complete	35	0	5	19	11 (31 per cent of 35)
Total	114	1	7	28	78 (68 per cent)

TABLE 5. *Duration of lesion.* All lesions (transverse and miscellaneous)*

TIME	TRANSVERSE LESIONS				MISCELLANEOUS	TOTAL
	Total	Per cent of 114 transverse lesions	Incomplete	Complete		
Less than 3 months through 5 months	13	12	10	3	0	13
6 to 12 months	15	13	9	6	1	16
1 to 2 years (not including 2)	16	14	14	2	2	18
2 to 5 years	31	27	13	18	5	36
5 to more than 30 years	39	34	33	6	19	58
Indeterminate	0	0	0	0	2	2
Total	114	100	79	35	29	143

* Time between onset of lesion and transurethral resection of vesical neck.

TABLE 6. *Residual urine correlated with type of lesion*

LESION	CASES	NO RESIDUAL URINE	LESS THAN 100 CC	100 TO 200 CC	200 TO 500 CC	500 TO 1,000 CC	1,000 + CC	TOTAL OR COMPLETE RETENTION	SUPRAPUBIC TUBE, NOT DETERMINED
Transverse complete	35	0	1	3	17	9	1	2	2
Transverse incomplete	79	0	13	16	32	14	3	0	1
Total transverse lesions	114	0	14	19	49	23	4	2	3
Miscellaneous	29	1	4	5	16	0	1	2	0
Grand total	143	1	18	24	65	23	5	4	3

Residual urine.—As has been emphasized in previous communications,[1–4] we believe that residual urine is the foremost problem involved in the study and care of the neurogenic bladder. It has been our experience that it presents the chief problem in a high percentage of patients with cord bladder. Its successful elimination helps greatly to protect the patient from death due to urinary sepsis. In table 6 the quantity of residual urine found in each case is correlated sclerosis 5; degenerative lesions of the spinal cord 5; arachnoiditis 3; amyotrophic lateral sclerosis 1, and Parkinson's disease 1.

Completeness of transverse lesions: Definition of terms.—It became apparent early in the study of the 114 cases with transverse lesions of the spinal cord that from the standpoint of preoperative analysis, as well as results, the cases fell into two distinct groups which we have labeled 1) incomplete (ambulatory) and 2) complete (nonambulatory). Although it may be difficult to make a hard and fast rule concerning such a division of patients, from a working standpoint the distinction is easily made. In the group of *incomplete lesions* were placed those patients whose original lesion may not have resulted in complete paralysis or those whose original lesion had caused complete paralysis but whose subsequent recovery had allowed them partial use of the paralyzed extremities. For the most part these were the patients who could hobble around with crutches and canes, with a varying degree of spastic, shuffling gait. In the group of *complete lesions* were placed those in whom the paralysis below the lesion was complete and no recovery had occurred. These patients are ordinarily called bed patients, a term which is no longer applicable, as many have been taught to move themselves about by the use of their arms and shoulders and with various types of swinging gaits with crutches and other walking aids. In this group of 114 transverse lesions, 35 were regarded as complete and 79 as incomplete.

TABLE 3. *Etiology of 114 transverse lesions correlated with completeness of the lesions*

ETIOLOGY	TOTAL	COMPLETE	INCOMPLETE
Traumatic	64	24	40
Inflammatory	23	7	16
Postoperative cord tumor or disk	20	4	16
After spinal anesthesia	7	0	7
Total	114	35	79

In tables 3 and 4 an attempt has been made to correlate the etiology and level of the transverse lesions with the completeness of the lesion. It is interesting to note (table 3) that practically all of the lesions resulting from spinal anesthesia or operations on the spinal cord for tumor and disk were incomplete lesions. Regarding the level of the lesion, it is apparent (table 4) that the lower the level of the lesion, the greater is the chance of the lesion being incomplete or of subsequent partial recovery to an "incomplete" stage. As would be expected in a group composed primarily of civilian patients, the lesion in 68 per cent of these 114 cases was located at T12 or below; 85 per cent of the 79 incomplete lesions were located at T12 or below; whereas only 31 per cent of the 35 complete lesions were at this level.

Duration of the cord lesion.—As was mentioned in the beginning of this paper, our work has been primarily directed toward the chronic stage of this disease. In the great majority of cases the standard methods of conservative treatment have been given a trial before the patients were seen by us, so that the chronic pattern of the vesical dysfunction has been established. These data appear in table 5, in which it can be seen that in approximately 75 per cent of the patients with transverse lesions more than a year had elapsed between the time of onset of the neurologic lesion and transurethral resection of the vesical neck.

TABLE 4. *Transverse lesions (114 cases). Level of lesion: complete and incomplete*

LESION	CASES	LEVEL OF LESION			
		Widespread or indefinite	Cervical	Thoracic	T12 and below
Incomplete	79	1	2	9	67 (85 per cent of 79)
Complete	35	0	5	19	11 (31 per cent of 35)
Total	114	1	7	28	78 (68 per cent)

TABLE 5. *Duration of lesion.* All lesions (transverse and miscellaneous)*

TIME	TRANSVERSE LESIONS				MISCELLANEOUS	TOTAL
	Total	Per cent of 114 transverse lesions	Incomplete	Complete		
Less than 3 months through 5 months	13	12	10	3	0	13
6 to 12 months	15	13	9	6	1	16
1 to 2 years (not including 2)	16	14	14	2	2	18
2 to 5 years	31	27	13	18	5	36
5 to more than 30 years	39	34	33	6	19	58
Indeterminate	0	0	0	0	2	2
Total	114	100	79	35	29	143

* Time between onset of lesion and transurethral resection of vesical neck.

TABLE 6. *Residual urine correlated with type of lesion*

LESION	CASES	NO RESIDUAL URINE	LESS THAN 100 CC	100 TO 200 CC	200 TO 500 CC	500 TO 1,000 CC	1,000 + CC	TOTAL OR COMPLETE RETENTION	SUPRAPUBIC TUBE, NOT DETERMINED
Transverse complete	35	0	1	3	17	9	1	2	2
Transverse incomplete	79	0	13	16	32	14	3	0	1
Total transverse lesions	114	0	14	19	49	23	4	2	3
Miscellaneous	29	1	4	5	16	0	1	2	0
Grand total	143	1	18	24	65	23	5	4	3

Residual urine.—As has been emphasized in previous communications,[1–4] we believe that residual urine is the foremost problem involved in the study and care of the neurogenic bladder. It has been our experience that it presents the chief problem in a high percentage of patients with cord bladder. Its successful elimination helps greatly to protect the patient from death due to urinary sepsis. In table 6 the quantity of residual urine found in each case is correlated with the type and completeness of the cord lesion. It is significant that in only 12 per cent of the 114 cases with transverse lesions was there less than 100 cc of residual urine, whereas in 68 per cent there was more than 200 cc. It is our impression that the gravity of this phase of the problem of neurogenic vesical dysfunction has not been fully appreciated.

Classification of preoperative vesical dysfunction.—We now come to the most difficult part of a study of this kind. It is obvious that if there were some accurate method of classifying types of neurogenic vesical dysfunction, it would not be difficult to correlate them with results of treatment. In this manner the relative chance of help by transurethral resection could be predicted preoperatively so that an intelligent selection of patients for operation could be made. Many classifications of neurogenic vesical dysfunction have been made, chiefly on the basis of cystometry. Our attempts to make practical use of cystometry in this regard have been disappointing.

Many meaningless descriptive terms have crept into the literature devoted to this subject. For instance, let us examine two of these terms; namely, "automatic bladder" and "overflow incontinence." If a bladder evacuates involuntarily at intervals exceeding one hour, leaving a residual urine of less than 3 fluid-ounces (about 90 cc), most of us would be content to call it an automatic bladder. Suppose the interval between evacuations were only 15 minutes or 10 minutes, and the residual urine amounted to 300 cc or 800 cc. Would the condition be called an automatic bladder or overflow incontinence? Again, given a patient with involuntary spurts of urine, the interval between which is irregular, say from five to thirty minutes, suppose the residual urine amounts to 50 cc. Is the condition then a reflex bladder? But if the residual urine were 200 cc, or 500 cc, or 1,000 cc, would the condition then be classed as "overflow incontinence in a nonreflex bladder"? Although classifications on paper look simple, the clinical problem, in our experience, is most complex and disturbing.

We have reviewed these 143 cases in a most critical manner, hoping to be able to discern factors which would offer some basis for a classification of preoperative vesical dysfunction. In this review it has been necessary to use the description of the type of vesical dysfunction given by the consultant caring for the patient. The results of this study have been a division of cases into six groups as far as the type of preoperative vesical dysfunction is concerned. It is obvious that the dividing lines between these groups are not well defined, and in many cases it has been difficult to decide into which group a case should be placed. It is interesting to note the similarity of our grouping to the types of vesical dysfunction described by Martin and Davis.[19] The best that we have been able to do in this regard is represented by the six following classes:

Type A. Automatic reflex bladder (at least 1-hour interval between involuntary evacuations of urine).

Type B. Frequent involuntary spurts of varying amounts of urine at irregular intervals.

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[19] Martin, J. and Davis, L.: Studies upon spinal cord injuries. I. The development of automatic micturition. Ann. Surg., 126: 472–477, 1947.

Type C. Urgency, urgency incontinence and precipitate type of micturition.

Type D. Distended bladder; patient strains to void.

Type E. Obstructive urinary symptoms, simulating symptoms of simple obstruction of the vesical neck.

TABLE 7. *Type of preoperative vesical dysfunction correlated with level of lesion and amount of residual urine (79 cases: incomplete transverse lesions)*

TYPE OF PREOPERATIVE VESICAL DYSFUNCTION	RESIDUAL URINE	TOTAL CASES	LEVEL OF LESION			
			Widespread	Cervical	Thoracic	T12 and below
A. Automatic reflex bladder (at least 1-hour interval between involuntary evacuations of urine)	From 150 to 200 cc	5	0	0	1	4
B. Frequent involuntary spurts of varying amounts of urine at irregular intervals	3:less than 100 cc 2:100 to 200 cc 14:200+	19	0	0	1	18
C. Urgency, urgency incontinence and precipitate type of micturition	7:less than 100 cc 8:100 to 200 cc 15:200+	30	0	2	5	23
D. Distended bladder; patient strains to void	3:less than 100 cc 3:100 to 200 cc 17:200+	23	1	0	2	20
E. Obstructive urinary symptoms, simulating simple vesical neck obstruction		0	0	0	0	0
F. Complete retention with pain; patient is unable to pass urine, either voluntarily or involuntarily		0	0	0	0	0
G. Vesical symptoms not accurately determined. Suprapubic tube in place	?	2	0	0	0	2
Total.............................		79	1	2	9	67

Type F. Complete retention with pain; patient is unable to pass urine, either voluntarily or involuntarily.

In tables 7 and 8 an attempt has been made to correlate these six types of vesical dysfunction with the level and completeness of the 114 transverse lesions, as well as the amount of residual urine present. In table 9 a similar correlation has been made in the 29 cases with miscellaneous lesions. Although, as stated previously, the classification of preoperative vesical dysfunction is admittedly crude, some interesting and instructive deductions may be drawn from these tables. It would seem logical to consider the data for each of the six types of preoperative vesical dysfunction enumerated previously.

TABLE 8. *Type of preoperative vesical dysfunction correlated with level of lesion and amount of residual urine (35 cases: complete transverse lesions)*

TYPE OF PREOPERATIVE VESICAL DYSFUNCTION	RESIDUAL URINE	TOTAL CASES	LEVEL OF LESION			
			Widespread	Cervical	Thoracic	T12 and below
A. Automatic reflex bladder (at least 1-hour interval between involuntary evacuations of urine)	1:less than 100 cc 3:100–200 7:200 and more	11	0	2	6	3
B. Frequent involuntary spurts of varying amounts of urine at irregular intervals	All more than 200 cc	17	0	3	8	6
C. Urgency, urgency incontinence and precipitate type of micturition		0	0	0	0	0
D. Distended bladder; patient strains to void	All 500 to 800 cc	3	0	0	2	1
E. Obstructive urinary symptoms, simulating simple vesical neck obstruction		0	0	0	0	0
F. Complete retention with pain; patient is unable to pass urine, either voluntarily or involuntarily	All residual	2	0	0	1	1
G. Vesical symptoms not accurately determined. Suprapubic tube in place	?	2	0	0	2	0
Total		35	0	5	19	11

Type A. Automatic reflex bladder (at least 1-hour interval between involuntary evacuations of urine):—This type of vesical dysfunction was encountered in only 6 per cent of the 79 incomplete and 31 per cent of the 35 complete transverse lesions. This seems rather surprising in view of the fact that we were dealing in this study primarily with the chronic phase of the disease. One would surmise from the literature concerning the subject that a fairly efficient automatic bladder occurs more often than this. Also in our series it may be seen (tables 7 and 8) that it occurred just as often when the lesions were low in the lumbosacral cord (T12 or below) as when they were higher. (General opinion has suggested that the automatic type of bladder should not result when the lesion is low enough to involve the reflex center for micturition.) Also, (contrary to general opinion) in most of our cases of automatic bladder there was a large amount of residual urine. This was especially true of the complete transverse lesions.

TABLE 9. *Miscellaneous lesions. Type of preoperative vesical dysfunction correlated with cause of lesion*

TYPE OF PREOPERATIVE VESICAL DYSFUNCTION	RESIDUAL URINE	TOTAL CASES	CAUSE OF LESION					
			Multiple sclerosis	Combined sclerosis	Degenerative cord lesion	Arachnoiditis	Amyotrophic lateral sclerosis	Parkinson's disease
A. Automatic reflex bladder (at least 1-hour interval between involuntary evacuations of urine)	300 cc	1	0	0	1	0	0	0
B. Frequent involuntary spurts of varying amounts of urine at irregular intervals	1: less than /100 cc 3:more than 200 cc	4	3	0	0	1	0	0
C. Urgency, urgency incontinence and precipitate type of micturition	2:less than 100 cc 3:100 to 300 cc 4:200+	9	6	1	1			1
D. Distended bladder; patient strains to void		1	1					
E. Obstructive urinary symptoms, simulating simple vesical neck obstruction	2:less than 100 cc 2:100 to 200 cc 7:200+	11	4	3	3	1		
F. Complete retention with pain; patient is unable to pass urine, either voluntarily or involuntarily	Complete retention	3		1		1	1	
G. Vesical symptoms not accurately determined. Suprapubic tube in place		0						
Total....................		29	14	5	5	3	1	1

Type B. Frequent involuntary spurts of varying amounts of urine at irregular intervals:—This is a very common type of neurogenic vesical dysfunction. It occurred in about 32 per cent (almost a third) of the 114 transverse lesions. It is somewhat more common in the complete than in the incomplete lesions, occurring in approximately one half of our complete and one fourth of our incomplete lesions. As can be seen from tables 7 and 8, there seems to be no correlation with the level of the lesion, as it was found with almost equal frequency with high and low lesions. Substantial amounts of residual urine (more than 200 cc) are the rule, although occasional cases are encountered with residual urine of less than 100 cc. This is the type of case that might be classified as an inefficient reflex automatic bladder if the residual urine is minimal, or an overflow incontinence if the amount of residual urine is great.

Type C. Urgency, urgency incontinence and precipitate type of micturition:—This is a very definite and typical form of vesical dysfunction, which is encountered only in incomplete transverse lesions (or complete lesions with partial recovery) and cases of miscellaneous lesions. It is not seen in patients with complete transection of the cord. It is the type of condition toward which our earliest therapeutic efforts with transurethral resection were directed. Also, it is the type of vesical dysfunction which responds most readily to transurethral resection. It was encountered in 38 per cent of our 79 cases of incomplete transverse lesions and 31 per cent of miscellaneous lesions (tables 7 and 9). There is no correlation with the level of the lesion, as it occurs with lesions at all levels. Substantial amounts of residual urine (more than 200 cc) are found in most cases. The typical patient with this difficulty is seen hobbling around on crutches or shuffling along with a spastic gait, with the aid of canes. He can get along fairly well except that he must wear a rubber urinal. He does not have dribbling incontinence. He gets the desire to urinate, but it comes so suddenly that he is unable to reach a toilet; so a urinal must be worn.

Type D. Distended bladder; patient strains to void:—This type of vesical dysfunction would seem to be of a nonreflex variety; yet it occurs with lesions at all levels in the cord. It occurred in less than 10 per cent of our cases of complete transverse lesions and almost 30 per cent of the cases of incomplete transverse lesions. There may be a little seepage of urine, but if the patient strains hard enough and frequently enough, he may be able to keep fairly dry.

Type E. Obstructive urinary symptoms, simulating symptoms of simple obstruction of the vesical neck:—This type of vesical dysfunction was confined to the miscellaneous lesions (table 9), where it was present in approximately 38 per cent of cases. As has been stated in previous communications,[4] because of the fact that the degenerative and other miscellaneous lesions of the cord are found in patients of an older age group, it is not always possible to decide how much of the urinary difficulty is on the basis of simple obstruction and how much is because of neurogenic disease. This fact may be partially responsible for this symptom complex, although the complex is also encountered in women with multiple sclerosis.

Type F. Complete retention with pain; patient is unable to pass urine, either voluntarily or involuntarily:—This is an unusual condition which was encountered in only 5 cases in our series. Two cases were found in the group of complete transverse lesions and 3 in the miscellaneous group. When present in the cases of transverse lesions, it is apparently the result of increased tonicity of the vesical neck and external sphincter, stimulated by troublesome extravesical reflexes.

Preoperative vesical dysfunction in cases of miscellaneous lesions:—It is of interest to consider the group of 29 miscellaneous lesions from the standpoint of preoperative types of vesical dysfunction. The most common varieties encountered were groups C (urgency, urgency incontinence and precipitate type of micturition) and E (obstructive urinary symptoms simulating simple obstruction of the vesical neck). These two types accounted for 20 of the 29 miscellaneous cases. (They accounted for 10 of the 14 cases of multiple sclerosis.)

Transurethral resection of the vesical neck.—Since the technique of transurethral resection of the vesical neck has been described elsewhere,[1–4] it will not be repeated here. It is of interest in the analysis of this group of cases to know the frequency with which multiple resections of the vesical neck are required. These data are shown in table 10. Approximately 29 per cent were done in multiple stages. As will be mentioned in the discussion of results, there may have been other patients who should have undergone more than one resection.

TABLE 10. *Number of resections per patient*

LESION	TOTAL NUMBER	1 STAGE	2 STAGES	3 STAGES	MORE THAN 3 STAGES
Incomplete	79	60	13	5	1
Complete	35	19	11	3	2
Miscellaneous	29	23	5	0	1
Total	143	102	29	8	4

Results of transurethral resection of the vesical neck.—As might be surmised, the accurate evaluation of results in this study has been almost as difficult as the classification of preoperative types of vesical dysfunction. We considered each case several times before deciding on its classification as far as results are concerned. We have tried to be most critical in our appraisal of these cases, realizing that the two most important factors to be corrected were 1) the residual urine and 2) urinary control. Here again, inaccurate terminology has caused confusion and difficulty.

After much trial and error, we decided to list results in three categories as follows: 1) Good: This indicates that the residual urine has been completely eliminated and that the patient has good urinary control. In the nonreflex type of bladder this may mean that the patient can initiate urination voluntarily with straining, and empty the bladder. In such a case, if a few drops of urine are lost when the patient is straining at violent exercise with a full bladder, it is still considered a good result. In other types of voiding it means that the patient has sufficient warning of micturition to allow time to reach a toilet or has sufficient control so that micturition can be postponed until a toilet can be reached. In many of the incomplete lesions with precipitate urgency incontinence the end result is, as far as can be determined, normal micturition. 2) Improved: Included in this group are cases in which a small amount of residual urine or some difficulty in control, or both, may persist. However, the improvement has been sufficient to more than justify the operative procedure. The importance of the results in this group should not be underestimated, as it includes some of the most grateful patients of the entire group. 3) Poor (unimproved): These are the cases in which the operation has not afforded sufficient relief to have warranted its use.

The results of transurethral resection for the entire group of 143 patients are listed in tables 11 and 12. Of the 114 transverse lesions, good results were obtained in 68 per cent, while 17 per cent more were improved. This makes a total of 85 per cent in which the operation seems to have been justified. If the results are considered on the basis of completeness of the lesion, some very interesting data are obtained. Of the 79 incomplete transverse lesions, good results were obtained in 80 per cent and 11 per cent more were improved, making a total of 91 per cent either good or improved. This makes a rather sharp contrast to the complete lesions, in which only 40 per cent good and 31 per cent improved results were obtained, making a total of 71 per cent either good or improved.

TABLE 11. *Results of transurethral resection of vesical neck in cases of transverse lesions of cord*

GROUPS	CASES	RESULTS							
		Good		Improved		Poor		Insufficient data	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Entire group transverse lesions.	114	77	68	20	17	15	13	2	2
Incomplete transverse lesions...	79	63	80	9	11	7	9	0	0
Complete transverse lesions....	35	14	40	11	31	8	23	2	6

TABLE 12. *Results in cases of miscellaneous lesions*

CASES	RESULTS							
	Good		Improved		Poor		Insufficient data	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
29	17	59	4	14	8	27	0	0

The results of transurethral resection in the 29 cases of miscellaneous lesions fell between those of the complete and the incomplete transverse lesions. Good results were obtained in 59 per cent, while another 14 per cent were improved, making a total of 73 per cent either good or improved.

Results correlated with level of lesion.—The results of transurethral resection have been compared with the level of the lesion in the 114 cases with transverse lesions (table 13). Little or no correlation was found. In our series of cases the level of the lesion seemed to be of minor importance.

Results correlated with type of preoperative vesical dysfunction and completeness of lesion.—In table 14 are listed the results of transurethral resection in the 114 cases of transverse lesions, correlated with the type of preoperative vesical dysfunction and the completeness of the lesion. It will be noted that the *most brilliant results* are achieved in groups C and D ("urgency and urgency incontinence," and "distended bladder; patient strains to void"), which in turn are found almost exclusively in the incomplete lesions. Good results were obtained in approximately 89 per cent of 53 cases of incomplete lesions in these categories. Good results were achieved also in both of the cases in group F (complete retention with pain), but the number is, of course, too small to be of statistical importance. *Next best results* were secured in group B (frequent involuntary spurts of varying amounts of urine at irregular intervals), in which approximately 58 per cent good results and 25 per cent improved results (total 83 per cent) were obtained in 36 such cases in which there were either complete or incomplete lesions. *The poorest results* have been obtained in group A (automatic bladder), in which only 38 per cent good and 31 per cent improved results were obtained. This substantiates the impression we have had for some time; namely, that our best results are obtained in the cases in which the bladders have a minimal amount of reflex activity and in which the patient can initiate urination at definite intervals by increasing the intra-abdominal and intravesical pressure by means of abdominal straining (if the abdominal muscles are intact) or manual compression.

TABLE 13. *Results in cases of transverse lesions (114 cases) correlated with level of lesion*

LEVEL	INCOMPLETE					COMPLETE				
	Total cases	Good	Improved	Poor	Insufficient data	Total cases	Good	Improved	Poor	Insufficient data
Widespread	1	1	0	0	0	0	0	0	0	0
Cervical	2	2	0	0	0	5	1	4	0	0
Thoracic	9	5	2	2	0	19	6	5	7	1
T12 and below	67	55	7	5	0	11	7	2	1	1
Total	79	63	9	7	0	35	14	11	8	2

Results in cases of transverse lesions correlated with cause and duration of lesion.—In table 15 an attempt has been made to correlate the results of transurethral resection in the 114 cases with transverse lesions, with the cause of the lesion and the interval of time elapsing between the onset of the neurologic lesion and the transurethral resection of the vesical neck. There is little that one can deduce from the traumatic and inflammatory cases in this table, other than to say that in the great majority of cases transurethral resection was not done until a year or more had elapsed after the cord injury. On the other hand, there

TABLE 14. *Results in 114 cases of transverse lesions correlated with type of preoperative vesical dysfunction and completeness of lesion*

TYPE OF PREOPERATIVE VESICAL DYSFUNCTION	INCOMPLETE TRANSVERSE LESIONS					COMPLETE TRANSVERSE LESIONS				
	Total cases	Good	Improved	Poor	Insufficient data	Total cases	Good	Improved	Poor	Insufficient data
A. Automatic reflex bladder (at least 1 hr. between involuntary evacuations of urine)	5	3	1	1	0	11	3	4	2	2
B. Frequent involuntary spurts of varying amounts of urine at irregular intervals	19	12	3	4	0	17	9	6	2	0
C. Urgency, urgency incontinence and precipitate type of micturition	30	25	5	0	0	0	0	0	0	0
D. Distended bladder; patient strains to void	23	22	0	1	0	3	0	0	3	0
E. Obstructive urinary symptoms, simulating simple vesical neck obstruction	0	0	0	0	0	0	0	0	0	0
F. Complete urinary retention with pain; patient is unable to pass urine, either voluntarily or involuntarily	0	0	0	0	0	2	2	0	0	0
G. Vesical symptoms not accurately determined. Suprapubic tube in place	2	1	0	1	0	2	0	1	1	0
Total...............	79	63	9	7	0	35	14	11	8	2

is considerable interest in the data concerning the cases of postoperative removal of cord tumors or protruded intervertebral disks, and also in the cases in which the lesion was the result of spinal anesthesia. In these cases excellent results were secured in 80 per cent of the postoperative lesions and in more than 70 per

TABLE 15. *Results in 114 cases of transverse lesions correlated as to cause and duration of lesion*

DURATION OF LESION	TRAUMATIC					INFLAMMATORY					POSTOPERATIVE CORD TUMOR OR DISK					SPINAL ANESTHESIA				
	Total cases	Good	Im-proved	Poor	Insuffi-cient data	Total cases	Good	Im-proved	Poor	Insuffi-cient data	Total cases	Good	Im-proved	Poor	Insuffi-cient data	Total cases	Good	Im-proved	Poor	Insuffi-cient data
Incomplete lesions																				
Less than 6 months	1	0	1	0	0	1	0	0	1	0	5	5	0	0	0	2	2	0	0	0
6 mo. to 1 yr. (does not include 1 yr.)	3	3	0	0	0	1	1	0	0	0	3	3	0	0	0	0	0	0	0	0
1 to 2 yr.	10	8	1	1	0	1	0	1	0	0	1	1	0	0	0	2	2	0	0	0
More than 2 yr.	26	21	2	3	0	13	11	2	0	0	7	5	1	1	0	3	1	1	1	0
Total.......	40	32	4	4	0	16	12	3	1	0	16	14	1	1	0	7	5	1	1	0
Complete lesions																				
Less than 6 months	1	0	1	0	0	0	0	0	0	0	2	1	0	1	0					
6 mo. to 1 yr. (does not include 1 yr.)	4	1	2	1	0	1	0	0	1	0	1	0	0	0	1					
1 to 2 yr.	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0					
More than 2 yr.	18	7	6	4	1	5	2	2	1	0	1	1	0	0	0					
Total.......	24	9	9	5	1	7	3	2	2	0	4	2	0	1	1					

cent of the lesions resulting from spinal anesthesia. Also, it may be noted that a large proportion of these patients underwent transurethral operation within a few months after onset of the lesion, indicating that in many cases the urologic disability may be corrected while the patient is still under observation for the neurologic surgical procedure.

Results in patients with small amounts of residual urine.—What results can be expected in patients who have small amounts of residual urine or none? Of the total of 143 cases (table 6), there were only 19 in which less than 100 cc of residual urine was present. Of these only 1 had no residual urine, 3 had ½ fluidounce (about 15 cc), while the remainder varied from 50 to 90 cc. One patient had a complete lesion, 13 had incomplete lesions and 5 were of the miscellaneous group. Type C (urgency incontinence) accounted for the type of preoperative vesical dysfunction in half of the cases. The results in the 19 cases were as follows: good, 14, improved, 4; poor, 1.

TABLE 16. *Miscellaneous lesions. Result of transurethral resection of the vesical neck correlated with cause of lesion*

LESION	TOTAL	GOOD	IMPROVED	POOR
Multiple sclerosis	14	7	4	3
Combined sclerosis	5	4	0	1
Degenerative cord disease	5	5	0	0
Arachnoiditis	3	0	0	3
Amyotrophic lateral sclerosis	1	1	0	0
Parkinson's disease	1	0	0	1
Total	29	17	4	8

Results in cases of miscellaneous lesions correlated with cause of lesion.—In table 16 are listed the results secured with transurethral resection in the various types of miscellaneous lesions. Except for multiple sclerosis, there are too few lesions in each group to be of any statistical importance. It is of interest that 50 per cent of the patients with multiple sclerosis secured good results, while another 29 per cent were improved. As has been emphasized previously, it is always difficult in this group to evaluate accurately the part played by simple obstruction of the vesical neck and that played by the neurogenic disease.

Permanency of results of transurethral resection: Late versus immediate results.—The results tabulated in the data analyzed in the preceding sections were the immediate results or those which had been obtained by the time the patient was dismissed to return home. We have been interested in knowing with what frequency results either improve or become worse as time passes. To this end letters of inquiry were sent to all patients whose operation had been done prior to 1948. We have follow-up data in 98 cases as given in table 1. Of the 98 cases in which follow-up data were obtained, later information caused us to change the classification of results in 23 cases, or approximately 23 per cent. Of the 23 patients, 14 became worse, while 9 improved, which would be a net change of approximately 5 per cent for the worse. Of the 14 patients whose condition became worse, 13 changed from good to improved, while 1 changed from good to poor. Of the 9 patients who improved, 3 changed from improved to good, 5 changed from poor to improved and 1 changed from poor to good. These data suggest that from a statistical point of view the immediate results portray fairly accurately the proportion of good, fair and poor results that may be expected.

The question is frequently asked as to what percentage of patients with immediate good results maintain those good results. Of the entire series of 143 cases good, immediate results were obtained in 93 cases (tables 11 and 12). Of these 93 cases follow-up studies were obtained in 79. Of these 79 cases in 65 (approximately 82 per cent) the good results were maintained. Thirteen changed from good to improved and 1 changed from good to poor.

Analysis of 14 cases in which immediate good results were not maintained.—It should be helpful to know why the immediate results are not maintained in some cases. Of the 14 patients whose condition became worse with the passage of time, 7 gave symptoms which suggest a recontracture of the vesical neck from scar tissue. It should be possible to re-establish good vesical function in these cases by another transurethral resection. The classification of results in 4 cases was changed from good to improved because the patient reported the development of various degrees of incontinence which were usually of either a stress or an urgency type. Two patients became worse because of progression of a malignant tumor of the spinal cord. One has a fairly efficient automatic bladder with a 2-hour interval between evacuations of urine, and 400 cc residual urine. After transurethral resection the residual urine is eliminated, but within a few months it recurs and another transurethral resection is necessary.

A selection of brief case abstracts illustrating the various types of vesical dysfunction, as well as the various types of results, may be helpful in understanding the general problem. They are included in the appendix.

SUMMARY

In the usual case of transverse lesion of the cord it would seem best to carry on with accepted conservative measures for several months or a year before advising transurethral resection. This waiting period allows time for any spontaneous recovery to occur and allows the chronic pattern of vesical dysfunction to be established. The exceptions to this rule are the incomplete lesions caused by operations on the spinal cord for tumor or protruded intervertebral disk, and also the rare lesions which result from spinal anesthesia. Patients in these cases have done well when transurethral resection is performed while the patient is still in the hospital convalescing from the operation on the spinal cord.

The level of the lesion in the cord seems to have little, if any, influence on the type of vesical dysfunction or on the results which might be expected from transurethral resection. The only important effect of the level of the lesion in this series of cases was that the higher the lesion the more likely it was to be a complete lesion with little or no recovery.

A satisfactory method of classifying neurogenic vesical dysfunction has not been devised. Cystometry has not been successful in our hands. A crude clinical classification into six types has been suggested in this paper. The overwhelming majority of all neurogenic bladders carry substantial amounts of residual urine.

By far the best results secured by transurethral resection in cases of transverse lesions of the cord have been in the group of incomplete lesions, in which 80 per cent good results and 11 per cent improved results were obtained. The *most brilliant results* have been achieved in the cases with the typical syndrome of urgency incontinence and precipitate urination so commonly found in incomplete transverse lesions.

Although the results are not as good for patients with complete lesions (37 per cent good results and 31 per cent improved) as for those with incomplete lesions, they are sufficiently good to justify putting forth the effort. The best results in the cases of complete lesions seem to be secured in patients whose vesical dysfunction we have classified as type B (frequent involuntary spurts of varying amounts of urine at irregular intervals). The poorest results are secured in cases of the true automatic bladder.

There seems to be no correlation between results of transurethral resection and the level of the lesion in the cord.

Moderately good results have been secured in the miscellaneous group of lesions, such as multiple sclerosis, combined sclerosis, degenerative lesions of the spinal cord, arachnoiditis, amyotrophic lateral sclerosis and Parkinson's disease. It is of interest that 7 good results were obtained in a small series of 14 cases of multiple sclerosis, while another 4 were improved.

There is not as much change between immediate and late results as has been supposed. Of 98 patients followed, a change for the worse was found in 14, while a change for the better was noted in 9, which makes the net change rather low. Of 79 patients with immediate good results who were followed, 82 per cent maintained their good results.

APPENDIX: ILLUSTRATIVE CASE ABSTRACTS GROUPED ACCORDING TO TYPE OF PREOPERATIVE VESICAL DYSFUNCTION

Type A. Automatic Reflex Bladder (at Least One-Hour Interval Between Involuntary Evacuations of Urine)

Case 1. Complete lesion; good result:—A woman aged 23 years had a traumatic lesion of 2½ years' duration at T8, with complete spastic paralysis. Involuntary urination occurred every 3 to 4 hours, without warning, at which time 200 to 300 cc of urine were evacuated, leaving a residual of 300 cc. Transurethral resection of the vesical neck was performed and 2 gm. of tissue were removed. The result was excellent. The patient now had some warning that she should void and *could initiate urination* and empty the bladder completely. There was no leakage of urine and no nocturnal incontinence if the patient was called twice during the night.

Case 2. Complete lesion; result improved:—A man aged 22 years had a gunshot wound at the level of T8, with complete paralysis. The lesion was of 2 years' duration. Involuntary urination occurred every 2 to 2½ hours. A slight ense of fullness in the lower part of the abdomen gave some warning of impending nicturition. The patient had 400 cc of residual urine. The bladder was markedly rabeculated, with a spastic, hyperplastic vesical neck. Transurethral resection was performed and 4 gm. of tissue were removed. The immediate result was that the patient still had an automatic bladder, with 2½ hours' interval between involuntary micturitions, but no residual urine was present. Twenty-seven months later, however, 360 cc of residual urine again were present. A second transurethral resection was done and 11.5 gm. of tissue were removed. Residual urine again was eliminated, but within four months it had recurred. The patient still had an automatic bladder with involuntary micturition.

Case 3. Complete lesion; poor result:—A man aged 44 years had inflammatory myelitis with complete paralysis 8 months before admission. The level of the lesion was at T9. Involuntary urination occurred at irregular intervals. There were multiple vesical calculi, for which litholapaxy was done. Afterward vesical dysfunction consisted of involuntary micturition without warning, every one and a half to three hours. The patient passed 2 to 4 fluid-ounces (about 60 to 120 cc) of urine each time, leaving 200 to 500 cc of residual urine. Transurethral resection was done in two stages, a total of 26 gm. of tissue being removed. Pathologic examination of the tissue showed adenofibromatous hyperplasia and inflammatory muscle. The result has not been good. Involuntary urination, at irregular intervals, has persisted, as well as residual urine. The patient catheterizes himself every 12 hours.

Type B. Frequent Involuntary Spurts of Varying Amounts of Urine at Irregular Intervals

Case 4. Complete lesion; good result.—A man aged 27 years had had a traumatic lesion of the spinal cord at level of D12 thirteen months before admission. There was complete spastic paraplegia. Vesical dysfunction consisted of irregular, intermittent, involuntary spurts of urine of varying amounts which occurred every few minutes *without warning*, leaving 300 cc of residual urine. After emptying the bladder completely with a urethral catheter, the patient would remain dry for one hour. There was marked trabeculation of the bladder and typical hypertonicity and hyperplasia of the vesical neck. Transurethral resection was performed, 6 gm. of tissue being removed. Pathologic examination showed adenofibromatous hyperplasia. The results were excellent. The patient now *has warning* of impending micturition and time to procure a urinal or reach a toilet. Micturition occurs every two to three hours and the bladder is emptied completely at each voiding. He has a normal urinary stream.

Case 5. Complete lesion; result improved:—A boy aged 18 years was admitted to the Clinic because of spastic paralysis of the lower extremities of 2 years' duration, which had resulted from inflammatory myelitis. The level of the lesion was T10. Vesical dysfunction consisted of involuntary spurts of 1 to 2 fluid-ounces (about 30 to 60 cc) of urine at irregular intervals of 10 to 30 minutes. Occasionally he evacuated a substantial amount, with a forceful stream. Residual urine was about 200 cc. The bladder was trabeculated, grade 2+ (on a basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition); the interureteric bar was hypertrophied, grade 3. Transurethral resection was done in two stages, and 11 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia and smooth muscle. Following this, anterior rhizotomy was done to control troublesome mass reflexes of the lower extremities. The anterior roots of the eleventh and twelfth thoracic, the first, second, third, fourth and fifth lumbar and the first and second sacral spinal nerves were severed. The patient is improved. Voiding is still involuntary, every one and a half to two hours. He empties his bladder completely, but cannot initiate urination. Since he has no warning of impending urination, he wears a urinal.

Case 6. Complete lesion; poor result:—A man aged 54 years was injured in an automobile accident 2 years before admission, at which time he sustained a transverse lesion of the cord, the level of which was T11 or L1. There was complete paralysis of the flaccid type. He had more or less constant leakage of urine. He could expel 2 to 3 fluid-ounces (about 60 to 90 cc) by abdominal straining. He had 300 cc of residual urine. The bladder was markedly trabeculated, with an obstructive collar at the vesical neck. Transurethral resection was done and 5 gm. of tissue were removed. The result was not good. Leakage continued when he moved or strained, although the amount of residual urine was much reduced.

Case 7. Incomplete lesion; good result:—A man aged 31 years sustained a traumatic lesion of the spinal cord 1½ years before admission. The level of the lesion was L1. He had partial recovery from the paralysis, with some motion of the legs, but flaccid paralysis below the knees, with drop foot. Involuntary spurts of urine occurred approximately every 30 minutes *without warning.* The patient had 250 to 300 cc of residual urine. He could expel some urine by abdominal straining and manual compression. Transurethral resection was done and 2 gm. of tissue were removed from the vesical neck. The result is good. The patient can void voluntarily and has a good stream, with abdominal straining. There is no residual urine and no leakage is present day or night.

Case 8. Incomplete lesion; result improved:—A man aged 44 years had a traumatic lesion of 5 years' duration. The level was L1. The patient experienced gradual partial recovery from paralysis, but motor and sensory changes were present in the lower extremities. He has learned to walk with leg braces and crutches. He had a suprapubic tube in place on admission. When the tube was clamped, the patient had frequent spurts of urine described as "overflow." He had 400 cc of residual urine. Transurethral resection was performed and 7 gm. of tissue were removed. Pathologic examination showed adenofibromatous hyperplasia. The patient's condition is improved. He can void at will, with abdominal straining, and empties his bladder completely. However, he has some stress incontinence on mild straining, which is controlled with a Cunningham incontinence clamp.

Type C. Urgency, Urgency Incontinence and Precipitate Type of Micturition

Case 9. Incomplete lesion; good result:—A man aged 61 years had been given continuous *spinal anesthesia* over a period of more than 2 hours for an abdominal operation, 1½ years before admission to the clinic. Since that time he had suffered with diminished sensation below the level of T12, and examination revealed hyperactive patellar and Achilles reflexes. There was no motor disturbance. Since the operation the patient had suffered from diurnal and nocturnal incontinence of the urgency type. If the patient voided every 30 minutes, he could keep dry most of the time. If he waited longer, severe urgency incontinence would ensue, with a poor, interrupted stream. Only 60 cc of residual urine were present.

The bladder was only slightly trabeculated. The vesical neck appeared dilated and relaxed, with a small, early trilobar prostatic enlargement, graded 1. Transurethral resection was performed, 5 gm. of tissue being removed. The result was excellent. The patient has voluntary and apparently normal micturition. He voids every two to three hours, with a good stream, and has no residual urine. There is no leakage of urine, day or night.

Case 10. Incomplete lesion; good result:—A man aged 57 years, 2 years before admission, had fallen 14 feet causing a transverse lesion of the cord at L1. Complete paralysis ensued, followed by partial recovery, so that he was able to walk with the help of crutches. He had marked urgency incontinence every 15 to 30 minutes, which required that he wear a rubber urinal. He voided 1 to 2 fluid-ounces (about 30 to 60 cc) each time, but left a residual of 300 cc. Transurethral resection was done, with removal of 10 gm. of tissue. The pathologic examination showed inflammatory muscle. The result was good. The patient voids every 1½ to 2 hours, with adequate warning to reach a toilet. He has no incontinence and no residual urine. He has nocturia every two hours.

Case 11. Incomplete lesion; result improved:—A man aged 40 years at the time of admission had undergone laminectomy with removal of a neurofibroma of the sixth thoracic spinal nerve at the age of 28 years. He had complete paralysis of the lower extremities before and after operation, with gradual recovery. At the time of admission he was able to get around well without canes or crutches, but continued to have trouble with his bladder and bowels and was impotent. The vesical dysfunction consisted of a poor, interrupted stream. He could initiate the stream by massaging the lower part of the abdomen. He had urgency incontinence, causing occasional soiling of his clothing. The residual urine varied from 50 to 100 cc. There were trabeculation of the bladder and spastic contracture of the vesical neck. Transurethral resection was done and 3 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia. The patient's condition was improved. He voids more easily, with only occasional urgency incontinence. Residual urine is 30 cc. It would seem that another transurethral resection might be indicated.

Type D. Distended Bladder; Patient Strains to Void

Case 12. Incomplete lesion; good result:—A man aged 21 years was wounded with a machine gun bullet during the Second World War, more than 2 years before admission. A cord lesion resulted, at the level of the cauda equina, causing immediate paralysis, from which he gradually recovered. Upon admission the only residual was a mild weakness of the left leg and some anesthesia of the basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition); the interureteric bar was hypertrophied, grade 3. Transurethral resection was done in two stages, and 11 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia and smooth muscle. Following this, anterior rhizotomy was done to control troublesome mass reflexes of the lower extremities. The anterior roots of the eleventh and twelfth thoracic, the first, second, third, fourth and fifth lumbar and the first and second sacral spinal nerves were severed. The patient is improved. Voiding is still involuntary, every one and a half to two hours. He empties his bladder completely, but cannot initiate urination. Since he has no warning of impending urination, he wears a urinal.

Case 6. Complete lesion; poor result:—A man aged 54 years was injured in an automobile accident 2 years before admission, at which time he sustained a transverse lesion of the cord, the level of which was T11 or L1. There was complete paralysis of the flaccid type. He had more or less constant leakage of urine. He could expel 2 to 3 fluid-ounces (about 60 to 90 cc) by abdominal straining. He had 300 cc of residual urine. The bladder was markedly trabeculated, with an obstructive collar at the vesical neck. Transurethral resection was done and 5 gm. of tissue were removed. The result was not good. Leakage continued when he moved or strained, although the amount of residual urine was much reduced.

Case 7. Incomplete lesion; good result:—A man aged 31 years sustained a traumatic lesion of the spinal cord $1\frac{1}{2}$ years before admission. The level of the lesion was L1. He had partial recovery from the paralysis, with some motion of the legs, but flaccid paralysis below the knees, with drop foot. Involuntary spurts of urine occurred approximately every 30 minutes *without warning*. The patient had 250 to 300 cc of residual urine. He could expel some urine by abdominal straining and manual compression. Transurethral resection was done and 2 gm. of tissue were removed from the vesical neck. The result is good. The patient can void voluntarily and has a good stream, with abdominal straining. There is no residual urine and no leakage is present day or night.

Case 8. Incomplete lesion; result improved:—A man aged 44 years had a traumatic lesion of 5 years' duration. The level was L1. The patient experienced gradual partial recovery from paralysis, but motor and sensory changes were present in the lower extremities. He has learned to walk with leg braces and crutches. He had a suprapubic tube in place on admission. When the tube was clamped, the patient had frequent spurts of urine described as "overflow." He had 400 cc of residual urine. Transurethral resection was performed and 7 gm. of tissue were removed. Pathologic examination showed adenofibromatous hyperplasia. The patient's condition is improved. He can void at will, with abdominal straining, and empties his bladder completely. However, he has some stress incontinence on mild straining, which is controlled with a Cunningham incontinence clamp.

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Type D. Distended Bladder; Patient Strains to Void

Case 12. Incomplete lesion; good result:—A man aged 21 years was wounded with a machine gun bullet during the Second World War, more than 2 years before admission. A cord lesion resulted, at the level of the cauda equina, causing immediate paralysis, from which he gradually recovered. Upon admission the only residual was a mild weakness of the left leg and some anesthesia of the posterior aspect of the buttock and thigh. The patient had a suprapubic tube in place. Previous transurethral resection had not enabled him to void. When the suprapubic tube was clamped, the bladder became distended; the patient strained to void, but only a few cubic centimeters of urine would pass. The trabeculation of the bladder was graded 2, and some postoperative irregularity of the prostatic urethra was present. Transurethral resection was done and 6 gm. of tissue were removed. The pathologist reported inflammatory muscle. Surgical closure of the suprapubic incision was carried out. The result was good. The patient voids normally and voluntarily, with a normal desire to void. He has no residual urine, no leakage of urine and no nocturia.

Case 13. Incomplete lesion; good result:—A woman aged 23 years had had inflammatory myelitis 10 years previous to admission. The immediate result had been quadriplegia. There was gradual recovery until upon admission the upper extremities were normal, but partial spastic paraplegia of the lower extremities remained. The patient walked with a spastic gait. There was weakness of muscles innervated below T9. The patient was unable to empty her bladder. She strained and "pounded" the suprapubic area to promote evacuation of urine. Residual urine never had been less than 400 cc. Her distended bladder might evacuate urine at any time, without warning. She required frequent catheterization and had frequent episodes of chills and fever. The bladder was trabeculated, grade 2, with spasticity and hyperplasia of the vesical neck. Transurethral resection was done, in multiple stages, over a period of several months. A total of 13 gm. of tissue was removed. The result was good. The patient voids voluntarily and empties her bladder completely. She has no leakage and no nocturia. She is able to teach school.

Case 14. Incomplete lesion; result improved:—A man aged 55 years was admitted to the Clinic because of back pain, sensory and motor changes in the lower limbs, and rectal and vesical "incontinence," which were found to be caused by a tumor of the spinal cord at the level of L1. Laminectomy and resection of an ependymoblastoma of the cauda equina was performed. The bladder was distended and the patient strained to evacuate a small amount of urine. The leakage was interpreted as being due to "overflow." He had 400 cc of residual urine. Transurethral resection was done and 9 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia. The immediate result was that the patient voided every two hours by the clock. He had no sensation of a desire to void. He used abdominal straining and had no residual urine. There was some incontinence on straining and moving around, which was controlled by a Cunningham incontinence clamp.

Case 15. Incomplete lesion; poor result:—A man 53 years of age was admitted to the Clinic complaining of pain in the lower part of the back, numbness and progressive weakness of the lower extremities, and difficulty in urinating and moving his bowels. The patient had a shuffling, unsteady gait, with spasticity of the lower extremities. A tumor of the spinal cord was found at the level of the fourth thoracic vertibra, for which laminectomy was done. Biopsy was performed and the tumor was found to be an ependymoma. Roentgen therapy was administered. The patient was unable to void, the bladder was distended, and he could evacuate only a few drops with straining. He had 1,000 cc of residual urine. Transurethral resection was done and 6 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia. The result was poor. There were frequent dribbles of urine, with 550 cc of residual urine. A second resection would seem to have been indicated.

Type E. Obstructive Urinary Symptoms Simulating Symptoms of Simple Obstruction of the Vesical Neck

Case 16. Multiple sclerosis; good result:—A man aged 40 years was admitted to the clinic because of visual disturbances, ataxia and difficulty in voiding. A diagnosis of multiple sclerosis was made. The vesical dysfunction consisted of a small stream, with frequency, nocturia of two to three times, and occasional dysuria. There were 450 cc of residual urine present. The bladder was only slightly trabeculated and there was a slight collar at the vesical neck. Transurethral resection was done and 6 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia. The result was excellent. The patient voided well and emptied his bladder completely.

The patient returned for re-examination 8 months later. He felt improved generally and stated that he could walk much better. He also stated that he was voiding without trouble. A check of residual urine, however, disclosed 350 cc to be present again. Transurethral resection was again done and 7 gm. of tissue were removed. The pathologic report was adenofibromatous hyperplasia. The result is good. The patient voids well and empties his bladder completely.

Type F. Complete Retention with Pain; Patient is Unable to Pass Urine, Either Voluntarily or Involuntarily

Case 17. Complete lesion; good result:—A man aged 41 years was admitted to the clinic because of complete paralysis of the lower extremities, which had resulted from inflammatory myelitis 6 years previously. The level of the lesion was the eighth thoracic vertebra. There was flaccid paralysis of the lower extremities. The patient had complete retention of urine. When the bladder distended, there was a vague sensation of pain in the abdomen but no urine escaped. The patient had been catheterized three or four times daily for the previous six years. There was trabeculation, grade 1+, of the bladder, with marked fixation of the vesical neck. Transurethral resection was done in two stages and about 6 gm. of tissue were removed. The pathologic report was inflammatory muscle. The result is good. The patient voids every three to four hours and can initiate urination voluntarily. He has a good stream, no residual urine and no leakage between voidings, unless he allows his bladder to become greatly overdistended.

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PARASITIC FIBROMYOMA OF THE BLADDER

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Benign mesothelial tumors of the bladder are rare but not unknown. The most common mesothelial tumors are those containing smooth muscle fibers in a fibrous stroma. They most commonly arise near the bladder neck and extend into the bladder. Occasionally, however, they may arise toward the periphery of the bladder wall and extend into the peritoneal space. Since the relative proportion of fibrous and muscular elements varies, the histopathologic classification likewise varies. As a result, these tumors are reported in the literature as myoma, fibromyoma, fibroid, etc., depending upon which elements are most prominent in the histology. Less than 50 authenticated cases of this type of tumor had been reported up to 1933, and since then less than a dozen have been reported.

This report is based upon a case which is unusual in addition to being one of these relatively rare tumors. As far as I have been able to determine, only one larger tumor of this type has been described. Furthermore, the resemblance of this tumor to a uterine fibroid is remarkable not only insofar as its histology is concerned but also in its apparent tendency to parasitism. It will be noted in the following case report that the symptoms were entirely due to the space consuming nature of the tumor. Organ systems, including the urinary tract, were affected only by displacement. The parasitic tendencies were indicated by the narrow vascular pedicle to the bladder associated with secondary vascular attachments to the omentum and left lateral abdominal wall.

CASE REPORT

B. E. M., a 58 year old, white male veteran, was admitted to the hospital because of a gradually enlarging mass in his abdomen, which he had noted for about 3 months. His past history was unremarkable until 6 years ago when he began to experience fainting spells, dependent edema and dyspnea. He was hospitalized at that time and treated for cardiac decompensation. Since then he had been hospitalized repeatedly for episodes of cardiac decompensation. However, except for these episodes of cardiac difficulty he got along fairly well until about 3 months ago when he first noticed a mild, generalized abdominal pain which was migratory in character and which did not localize to any one area. The only unusual feature about the pain was that walking, or rolling from side to side in bed, aggravated it and produced a dragging sensation within the abdomen. During these 3 months the pain gradually became worse and his abdomen became increasingly more protuberant. About a week previous to admission he consulted his local physician who palpated his abdomen, discovered a mass

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and referred him to the hospital. A review of the systems revealed no symptoms referable to the respiratory, cardiac or gastro-intestinal tracts. He did have urinary symptoms, particularly frequency of about 10 times a day and nocturia of 3 or 4 times. There had never been hematuria nor difficulty in starting or stopping the stream.

Physical examination revealed an alert, cooperative patient who did not appear acutely ill. He was ambulant and walked with a normal gait without assistance. The head and neck were negative with the exception of a small nodule in the right lobe of the thyroid. The chest was normal to inspection and palpation. No adventitious sounds were audible. The blood pressure was 126/70 and the heart was entirely normal to palpation, percussion and auscultation. The abdomen was markedly protuberant, having the general contour of a 7-month pregnancy. On palpation a large mass was discovered in the center of the abdomen which extended from the symphysis pubis up to the costal margin. The mass was nontender, had rounded edges and was slightly movable. Rectal examination revealed prostatic hypertrophy but the abdominal mass could not be palpated. A minimal degree of pitting edema was noted in the lower extremities. The diagnosis at this time was abdominal tumor, type unknown, mesenteric cyst, retroperitoneal sarcoma and abdominal Hodgkin's disease to be considered.

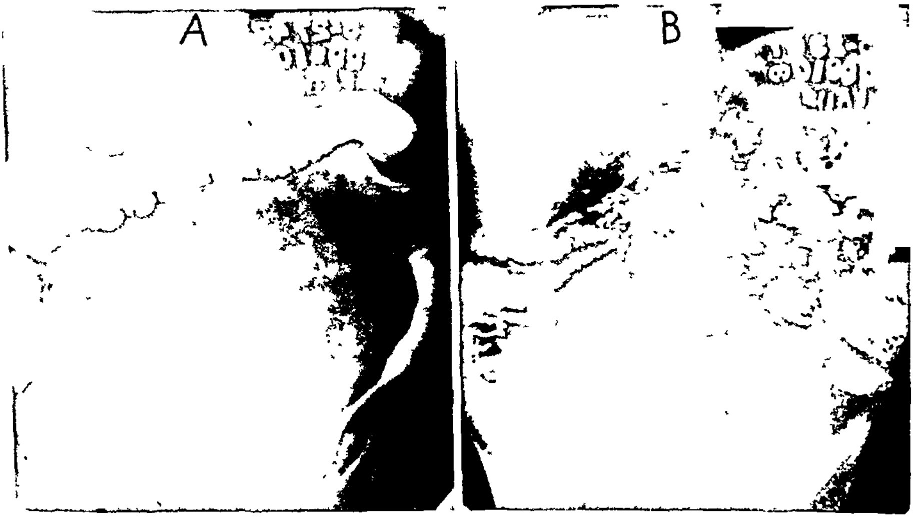

FIG 1. *A*, barium enema showing centrifugal displacement of colon with loss of normal sigmoid and transverse redundancy Superior edge of tumor is visible in left upper quadrant. *B*, gastro-intestinal roentgenogram following a barium meal showing displacement of small bowel pattern. Location of tumor is inferred by surrounding small bowel pattern.

The patient was studied completely. The blood count and blood chemistries were well within normal limits. The serology was negative. The urinalysis was normal. A phenolsulfonphthalein test showed normal function of the kidneys and a glucose tolerance test revealed a normal curve. The stool was positive for occult blood but no parasites could be found. A roentgenogram of the chest was normal. A flat film of the abdomen revealed a definite increase in the soft tissue density in the lower abdomen. However, with the exception of a moderate degree of spondylitis no definite conclusions could be reached by the roentgenologist. Roentgenograms of the gastro-intestinal tract revealed displacement of the bowel upward and laterally (fig. 1). There was no evidence of retention in the stomach and progression of the meal was normal. A barium enema (fig. 1, *A*) disclosed a colon which filled readily without obstruction but showed evidence of a large mass which displaced the sigmoid and the transverse portion of the colon. There was also some evidence of external pressure upon the distal portion of the descending colon. No intrinsic lesion of the colon was demonstrated. An excretory urogram was not completely satisfactory due to the increase in soft tissue density previously described (fig. 2). However, dye was faintly visualized in both kidneys and a bifid pelvis was discovered on the left. There was no evidence of obstruction but the dome of the bladder was flattened, apparently due to external pressure.

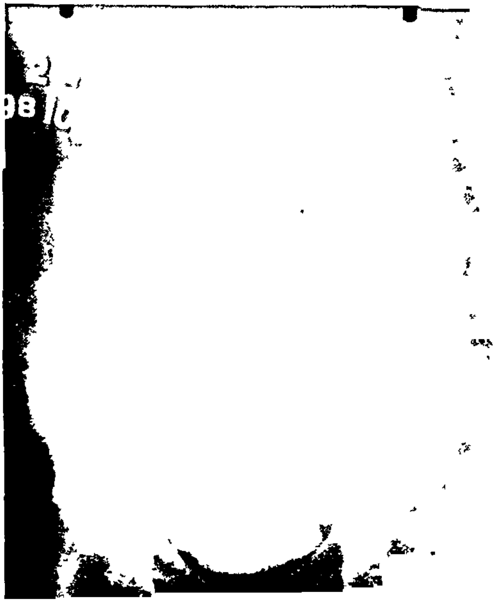

FIG 2 Excretory urogram showing marked increase in soft tissue density which obscures visualization of renal pelves. Flattening of dome of bladder is evident.

The patient was examined by the cardiologist who believed that, although the history of cardiac disease should be kept in mind, there was no evidence of cardiac decompensation and that surgery could be recommended. Accordingly, the patient was taken to the operating room and the abdomen was entered through a left paramedian incision which was made to extend from the symphysis pubis to approximately 4 cm. above the umbilicus. The left rectus muscle was retracted laterally. As soon as the abdomen was opened a large, nodular, yellow-gray tumor was discovered measuring approximately 20 by 10 cm. The tumor was attached to the bladder by a delicate pedicle which consisted of blood vessels and connective tissue with a peritoneal covering. There were additional vascular attachments, one in the left gutter, one to the greater omentum above and one to the omentum in the right lower quadrant in the area where adhesion had formed following a previous appendectomy. With the exception of these delicate vascular adhesions the tumor lay completely free in the abdomen. It was readily removed by dividing the adhesions and lifting it out of the abdomen. The area of attachment to the bladder was peritonealized and the abdomen was closed in layers. The patient was returned to the ward in good condition. A continuous spinal anesthetic was used.

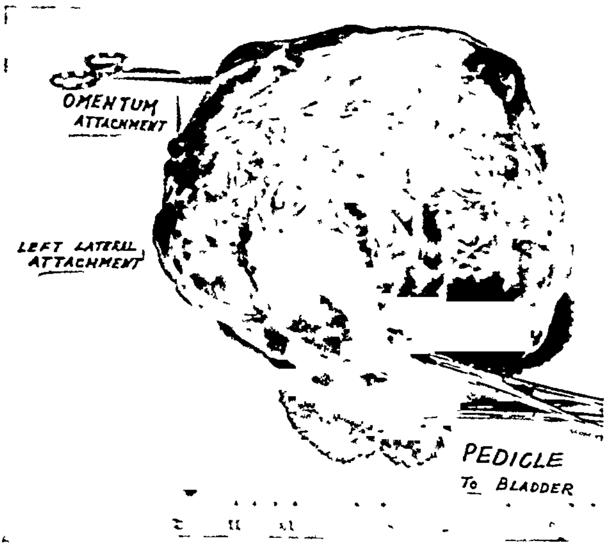

Fig 3 Gross specimen Points of vascular attachment are indicated. Parasitic nature of tumor is demonstrated in delicacy of vascular pedicles

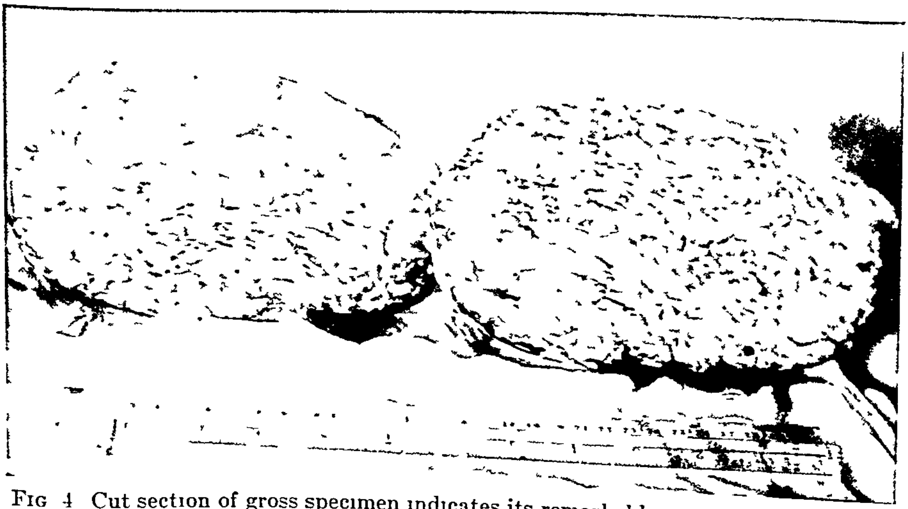

Fig 4 Cut section of gross specimen indicates its remarkable resemblance to a uterine fibroid

The pathologic report on the specimen was as follows: The gross specimen consists of a tumor mass which was well encapsulated and globular in shape (fig. 3). It measured 20.9 cm. across the long axis, 13.5 cm. through the short axis and weighed 3395 gm. The external surface was covered by a thin connective tissue membrane which was highly vascular and contained numerous tortuous blood vessels. Along one margin, extending for a distance of 8 cm., was an adherent remnant of omentum and opposite the margin to which the omentum was adherent was a short pedicle which extended from the tumor substance. The external surface of the tumor was extremely nodular giving a "hobnail" effect. These nodules were firm and the specimen cut with increased re-

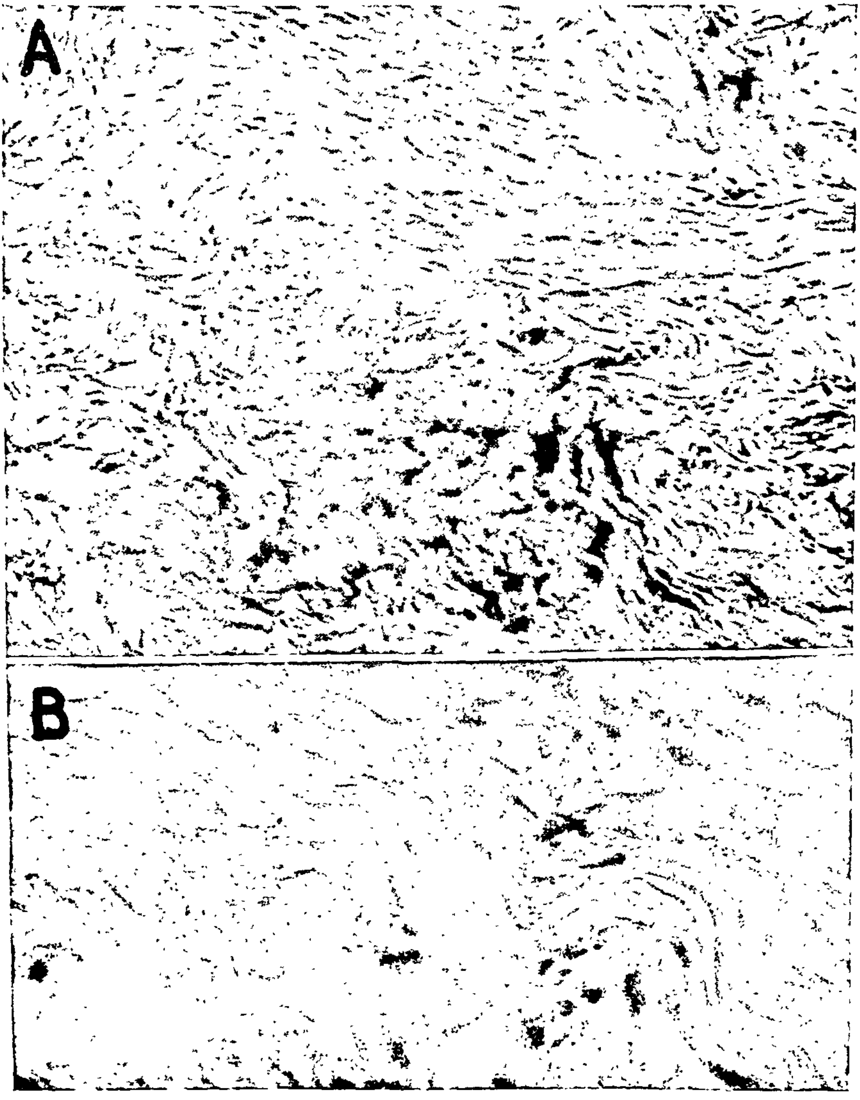

FIG. 5. Low and high power magnifications demonstrating histological characteristics of tumor. Spindle shaped cells arranged in whorls are noted.

sistance revealing a very irregular surface which grated under the knife blade. The cut surface was grey-pink in color mottled by glistening white areas which appeared to be branching strands of dense, fibrous, connective tissue (fig. 4). The tumor was quite vascular although no areas of hypervascularization or blood sinuses could be demonstrated.

Twenty histopathological sections were examined and found to be quite comparable. They revealed neoplastic, smooth muscle tissue which had assumed a very irregular formation, many whorls and branches being evident. This smooth muscle tissue was contained in a dense connective tissue stroma, in which areas of hyalinization and collagenous degeneration were demonstrable. The stroma was abundant and in some sections had completely replaced the muscle tissue. From the study of these sections it was believed that the tumor was benign, especially since examination of the pedicle showed no evidence of malignant degeneration. The comment by the pathologist was that "had this tumor occurred in a female the diagnosis would have been leiomyoma of the uterus." The pathological diagnosis was leiomyofibroma, benign (fig. 5).

The postoperative course was complicated by the development of superficial phlebitis in the right leg. This responded well to treatment and the patient was discharged ambulant on the twentieth postoperative day, being asymptomatic and having had a normal temperature for 4 days.

Three months later he was found to be in good health with the exception of heart disease. There was no evidence of recurrence of the tumor and an excretory urogram was again essentially normal with the exception of the previously noted bifid left renal pelvis.

SUMMARY

An unusual case of benign leiomyofibroma of the bladder is reported.

Although these tumors are not unknown they are relatively uncommon. This case is especially unusual because of the enormous size of the tumor and its remarkable resemblance to a parasitic fibroid of the uterus.

REFERENCE

Geisinger, J. F.: Fibroids of the urinary bladder. J. Urol., 29: 661-676, 1933.

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CARCINOMA OF THE BLADDER: CLINICAL, THERAPEUTIC AND PATHOLOGIC ASPECTS OF 135 CASES

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An analysis of 135 consecutive cases of carcinoma of the bladder, treated at Barnes Hospital, has been made to determine the late results of conservative treatment. In order to obtain a complete 5 year follow-up, no case after January 1943 was included. It was necessary to eliminate an additional 25 cases because no microscopic sections were available.

The study was divided into the following groups: 1) pathology, 2) size of tumor, 3) position of tumor, 4) vital statistics, 5) symptoms, 6) treatment, 7) survivals, and 8) autopsies.

PATHOLOGY

The tumors were classified according to their microscopic appearance. The sections of each lesion were carefully checked and graded as to the degree of malignancy without previous knowledge of the clinical course of the disease.

The transitional cell carcinomas were divided into 4 grades using criteria similar to that of Ash.

Grade 1 tumors. Regular frond-like papillary masses were seen. These masses of tumor cells were separated by evenly spaced connective tissue septa. Individual cells were uniform, transitional in appearance, and had rather abundant cytoplasm. Mitotic figures were few in number (fig. 1, *A* and *B*). Most of these lesions were pedunculated and villous, thus resembling the characteristic 'papilloma'. Twenty-six of the 38 tumors were pedunculated but only 22 of these were villous. Six were sessile and 4 were large and fungating, resembling a cauliflower in appearance. Some degree of necrosis was present in 6 of the cases.

Grade 2 tumors. The papillary nature of the tumor remained but the connective tissue septa were irregularly spaced and often embraced relatively large masses of cells. Vascularization was prominent. In some areas mitotic figures were frequent. The individual cells in some zones showed prominent homogeneous nuclei with little cytoplasm (fig. 2, *A* and *B*). Grossly, most of these lesions resembled the grade 1 tumors. As a whole, their bases were broader and their stalks shorter. Only a few had the villous appearance seen so frequently in the grade 1 lesions. Twelve of the 23 were pedunculated and 6 were sessile. Some degree of necrosis was present in 2.

Grade 3 tumors. Papillary areas were still present but patchy in distribution. The cells appeared to be breaking up into smaller groups and mitotic figures were often abundant (fig. 3, *A* and *B*). Grossly these tumors appeared, as a whole, to be much more malignant than the grade 1 and 2 tumors. Only 3 were pedunculated and none of these showed any degree of necrosis or ulceration. Eleven were sessile of which 1 was definitely necrotic and 2 ulcerated. Seven of the tumors were cauliflower-like in appearance.

Grade 4 tumors. Papillary areas were usually absent. Tumor cells were in small nests and could be recognized only because of the small homogeneous, deeply

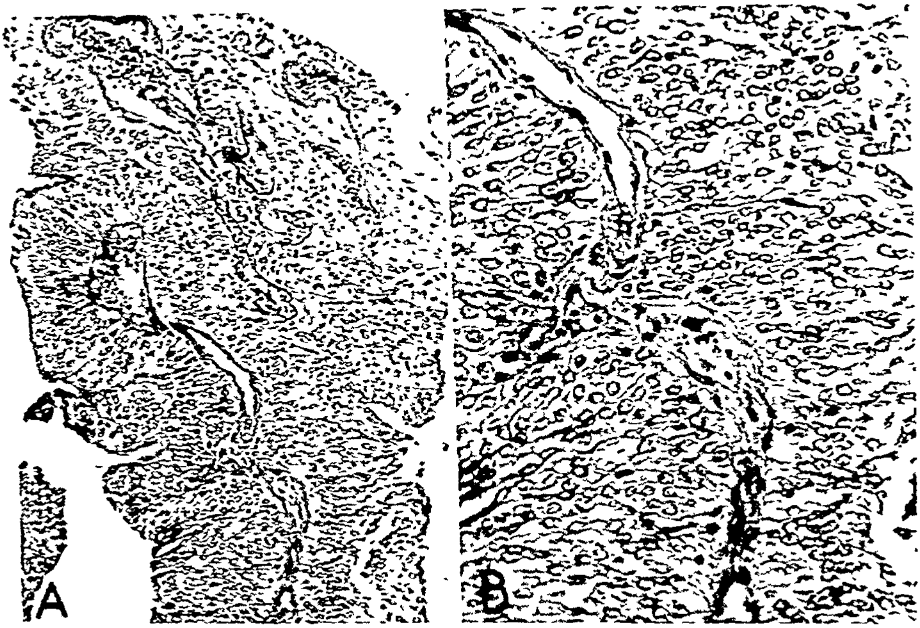

FIG 1 Transitional cell carcinoma grade 1. *A*, low power *B*, high power

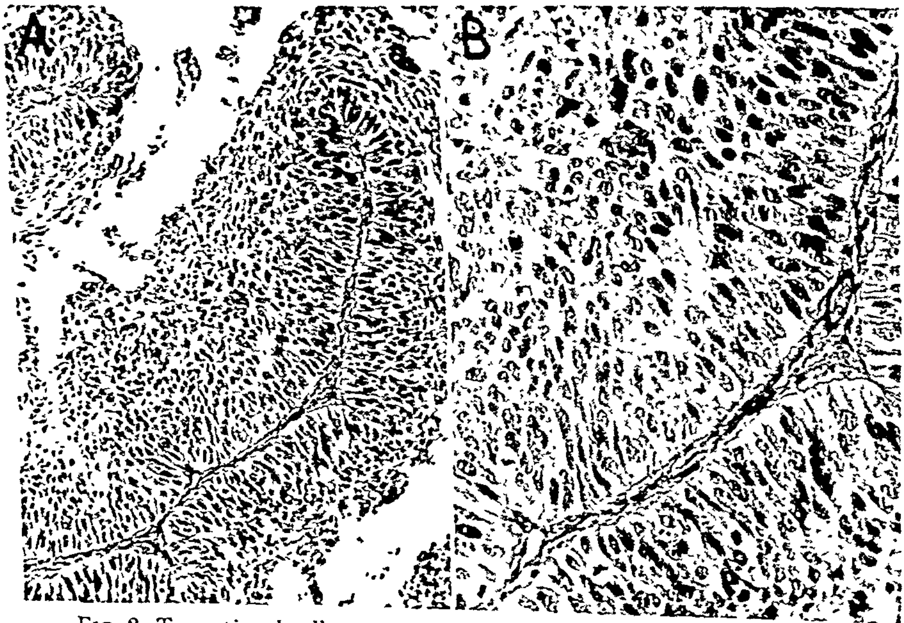

FIG 2 Transitional cell carcinoma grade 2. *A*. low power *B*, high power

blue-stained nuclei. Cytoplasm was small in amount and mitotic figures were frequent (fig. 4, *A* and *B*). Grossly, only 3 of the 25 tumors were pedunculated and 2 of these were necrotic. Thirteen were sessile, and of these, 2 were necrotic, and 3 were ulcerated. Four of the lesions were cauliflower-like in appearance.

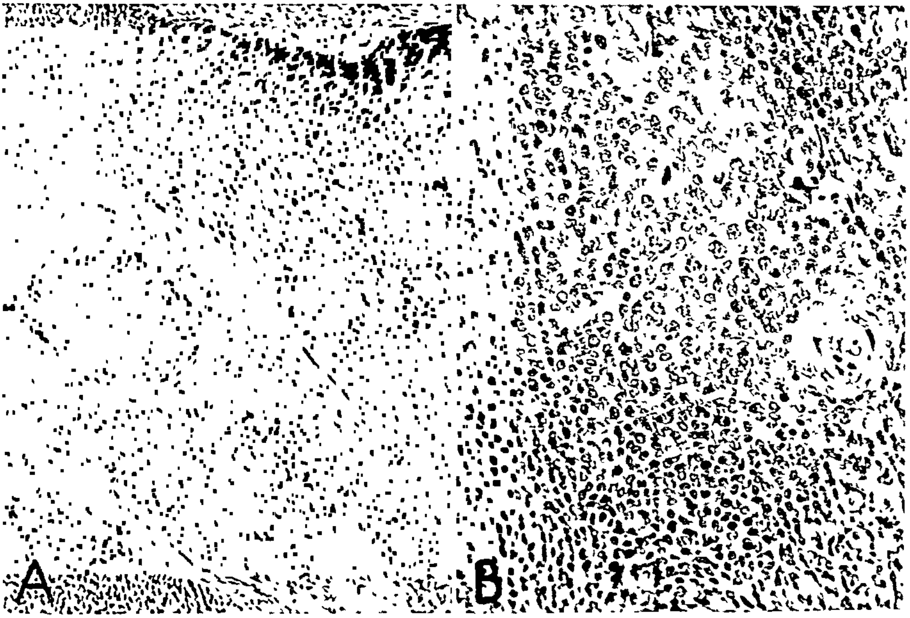

FIG. 3. Transitional cell carcinoma grade 3. *A*, low power. *B*, high power

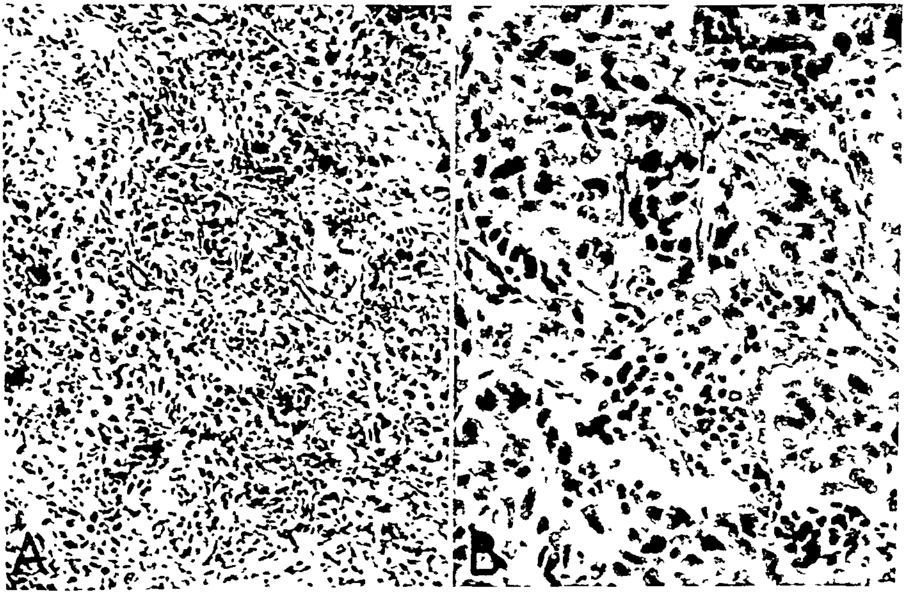

FIG. 4. Transitional cell carcinoma grade 4 *A*, low power *B*, high power

Undifferentiated carcinoma. The group which could not be classified was made up of undifferentiated epithelial neoplasms with possibly one exception. In some instances, an exact classification could not be made because the specimen was not adequate or previous treatment such as radiation obscured the microscopic pattern. However, the histiogenesis of this group is probably the same as that of the transitional cell tumors (fig. 5, *A* and *B*). All of these 11 lesions appeared grossly to be quite malignant; none were pedunculated; 7 were sessile, and 3 of these were necrotic and 4 ulcerated. Two of the lesions were cauliflower-like in appearance and 1 was incrusted with mineral material.

Squamous carcinoma. In every case, the tumor was an undifferentiated squamous neoplasm and was invariably associated with very prominent inflammation. In many instances, squamous metaplasia of the lining bladder epithelium accompanied the tumor (fig. 6, *A* and *B*). These tumors invaded the underlying bladder musculature, growing in small nests within the lymphatics, and at times, in the veins (fig. 6, *C* and *D*). These lesions, as a whole, had a more malignant infiltrating appearance grossly than the transitional cell tumors. All were associated with a marked degree of general inflammation of the entire bladder surface. Only 1 of the 12 was pedunculated and it was necrotic. Nine were sessile, of which 3 were necrotic and 1 ulcerated. One was cauliflower-like in appearance and 1 was incrusted with black mineral material and fibrin. These tumors were usually associated with a diminished bladder capacity, especially when the lesion was quite large.

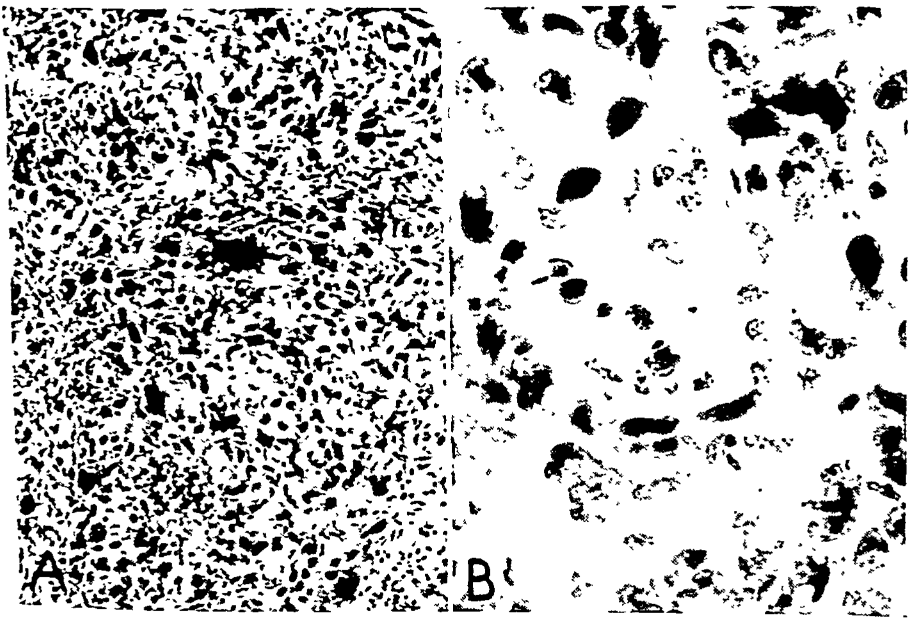

FIG. 5. Undifferentiated carcinoma. *A*, low power. *B*, high power

Unclassified carcinoma. One biopsy contained only a few viable malignant cells and could not be definitely placed in any of the above categories. Accordingly it was listed as an unclassified carcinoma.

Transitional cell carcinoma. Seven of the transitional cell carcinomas also contained areas of squamous carcinoma, but because the transitional was the predominant cell type they were listed as transitional cell.

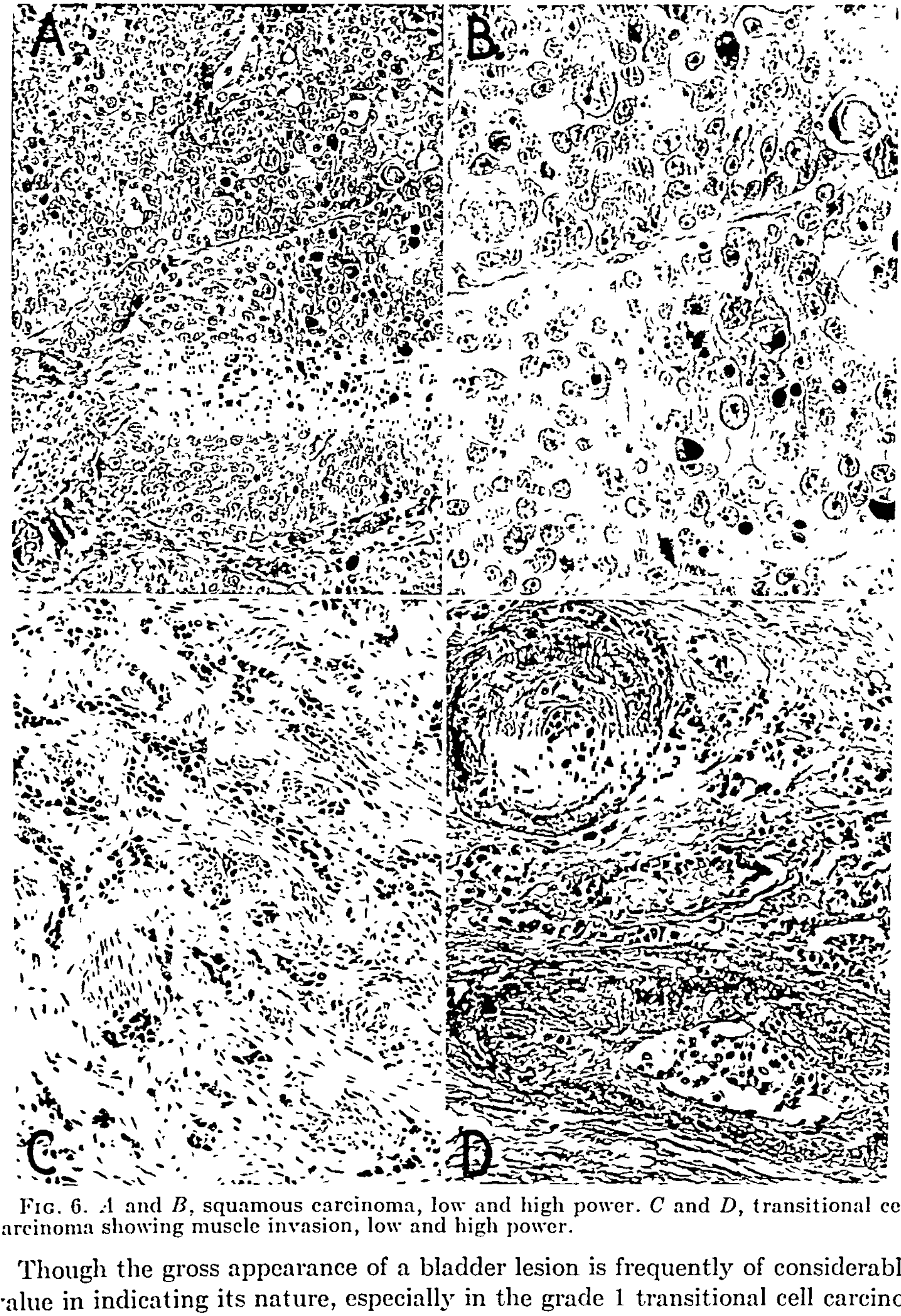

Fig. 6. *A* and *B*, squamous carcinoma, low and high power. *C* and *D*, transitional cell carcinoma showing muscle invasion, low and high power.

Though the gross appearance of a bladder lesion is frequently of considerable value in indicating its nature, especially in the grade 1 transitional cell carcinomas, it certainly is not a reliable criterion. This point is borne out by the fact that 6 of the grade 1 transitional cell carcinomas were sessile, necrotic and ulcerated, the appearance generally associated with lesions of a much higher grade of malignancy. On the other hand, 3 of the grade 3 transitional cell carcinomas were pedunculated without evidence of necrosis or ulcercation which is usually associated with tumors of a low grade of malignancy.

SIZE OF TUMOR

The size of the tumor was not well related to its degree of malignancy. For example, of the grade 1 transitional cell carcinomas, 37.5 per cent were less than 2 cm. in diameter and 22.2 per cent were over 5 cm. in diameter. As a whole, the more malignant tumors tended to be larger than those of low grade malignancy, but the difference was not sufficient to be significant. There was a much closer relationship between the size of the tumor and its prognosis. Tumors less than 2 cm. in diameter had an average survival of 4 years and 2 months. Those 2 to 4.9 cm. in diameter survived an average of 3 years and 4 months and those 5 cm. in diameter and over only 1 year and 6 months.

TABLE 1 *Gross appearance of bladder tumors*

	TRANSITIONAL CELL GRADES				SQUAMOUS	UNDIFFERENTIATED	TOTAL
	1	2	3	4			
Pedunculated	26	12	3	3	1	0	45
Not necrotic	22	10	3	1	0	0	36
Necrotic	4	2	0	2	1	0	9
Sessile	6	6	11	13	9	7	52
Necrotic	2	0	1	2	3	3	11
Ulcerated	1	0	2	3	1	4	11
Not stated	3	6	8	8	5	0	30
Cauliflower-like	4	1	7	4	1	2	19
Incrusted	0	0	0	0	1	1	2
Not stated	2	4	4	5	0	1	16
Total	38	23	25	25	12	11	134

TABLE 2. *Relationship between the size of tumor and its grade and prognosis*

	TRANSITIONAL CELL GRADES				SQUAMOUS	UNDIFF.	UNCLASS.	TOT.	AVE. SURV.
	1	2	3	4					
0–1.9 cm.	9	8	3	2	0	2	0	24	4 yr. 2 mo.
2–4.9 cm.	18	9	9	12	4	4	0	56	3 yr. 4 mo.
5 cm. and over	8	3	10	6	5	3	1	36	1 yr. 6 mo.
Not stated	3	3	3	5	3	2	0	1	

POSITION OF TUMORS

The positions of the tumors were tabulated in a manner similar to that of the Bladder Tumor Registry (fig. 7).

In many instances, the exact position of the tumor was not described. However, it was possible in most instances to place the tumor fairly definitely in one of the areas outlined figure 7. In the case of the large tumors occupying more than one area the central part was designated as its site of origin.

The transitional cell and the undifferentiated carcinomas had the same general distribution: approximately 75 per cent were located on the base or neck of the bladder (positions 1, 2, 3, and 4), whereas only 33 per cent of the squamous carcinomas were located there. The latter were located mostly on the dome and anterior bladder wall (7 out of 12). Interestingly enough, of the 6 tumors which involved virtually the entire surface of the bladder, 3 were of only grade 1 malignancy.

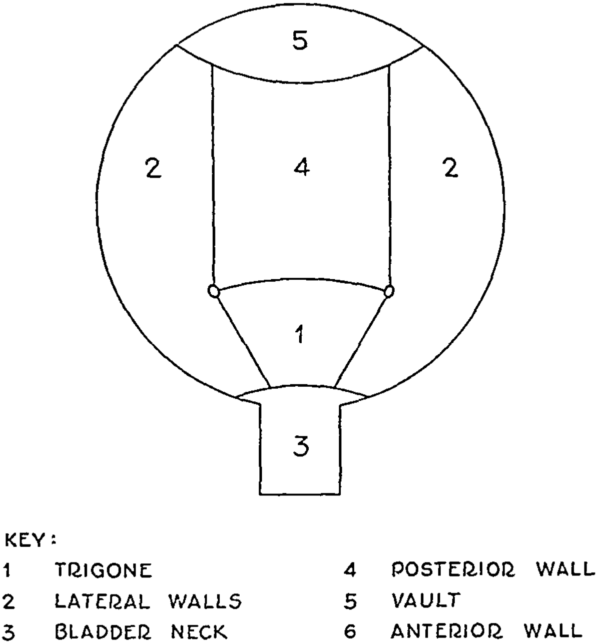

FIG. 7

There was a definite difference in the average degree of malignancy in different locations of the bladder. Of the 79 tumors located on the base, 49 (63 per cent) were grades 1 and 2 transitional cell carcinomas, whereas of the 23 tumors located on the dome and anterior surface, only 4 (17.4 per cent) were grades 1 and 2. Seven (30.4 per cent) of the 23 tumors on the dome and anterior surface of the bladder were squamous carcinomas, and 12 (52.2 per cent) were grade 3 and 4 transitional cell and undifferentiated carcinomas.

As would be expected, the prognosis of tumors located on the base of the bladder is much better than that of tumors on the dome and the anterior wall of the bladder. There were only 2 (11.8 per cent) 5 year survivals in the group of tumors on the dome and anterior wall of the bladder compared with 29 (34.5 per cent) 5 year survivals in the group located on the base of the bladder.

VITAL STATISTICS

The average age in the series was 60.8 years: the youngest patient being 39 and the oldest 82. Only 6 of the 135 patients were Negroes but the small number of Negroes in this series is not significant as only a few of the beds in this hospital are allotted to them. Ninety-four were male and 41 female. There was no mention made in any of the records as to whether the patients worked in aniline dye industries or not.

SYMPTOMS

Painful hematuria was the initial symptom in 36 patients, painless hematuria in 47, and dysuria not associated with hematuria was the initial symptom in 45. Twenty-one of the 47 patients who initially had only painless hematuria never developed dysuria prior to entering the hospital. Eighteen of the patients who initially had only dysuria had no history of gross hematuria before coming to the hospital, entering with the presumptive diagnosis of urinary infection, prostatism or calculi. One patient had no history of either hematuria or dysuria, having only frequency and nocturia. On routine cystoscopy the bladder tumor was discovered.

TABLE 3. *Relationship of location of tumor with degree of malignancy and prognosis*

POSITION	TRANSITIONAL CELL GRADES				SQUAM.	UNDIFF.	UN-CLASS.	TOT.	NO. 5 YR. SURV.	PER CENT 5 YR. SURV.	LOST
	1	2	3	4							
I	8	3	5	1	2	1	0	20	5	29.4	3
II	15	8	10	13	1	4	0	51	17	40.5	9
III	1	2	0	0	0	0	0	3	1	50.0	1
IV	7	5	3	5	1	3	1	25	6	26.1	2
V	2	1	2	2	4	2	0	13	2	16.7	1
VI	1	0	3	2	3	1	0	10	0	0.0	5
Entire bl	3	1	1	0	1	0	0	6	2	50.0	2
Not stated	1	3	1	2	0	0	0	7	0	0.0	3

There was a rather significant difference in the incidence of symptoms in the different types of tumors. In the tumors of low grade malignancy there was a predominance of hematuria in the symptomatology, whereas in the more malignant tumors there was a preponderance of dysuria.

The symptoms associated with these lesions correspond very closely to what would be expected from their pathologic appearances. The low grade malignancies were usually associated with very little or no infection, inflammation or necrosis which accounted for the small incidence of dysuria. Bleeding was more apt to occur because the tumors grew out into the bladder lumen, were rather vascular and were more subject to trauma and trophic changes. On the other hand, the tumors of high grade malignancy were frequently associated with dysuria which corresponds closely to the fact that they were almost all associated with infection and necrosis. Since they tended to grow into the wall of the bladder and infiltrate widely rather than grow out into the bladder lumen, they were not as subject to the trauma incident to voiding as were the tumors of low grade malignancy. Also, by infiltrating the detrusor muscle, the bladder was rendered less elastic and thus decreased in capacity, producing the symptoms of frequency and urgency.

Thirty-three (70.2 per cent) of the patients with an initial symptom of painless hematuria had tumors of only grade 1 or 2 malignancy. Only 12 (33 per cent) of the patients with an initial symptom of painful hematuria had tumors of grade 1 and 2 malignancy. Seventy-one per cent of the patients with an initial symptom of dysuria without hematuria had grades 3 and 4 transitional cell, undifferentiated and squamous carcinomas. All but 6 of these latter cases complained of dysuria before coming to the hospital. The incidence of hematuria was quite high (86 per cent) with all grades of tumors but the presence of dysuria was a dangerous sign as it was usually associated with a tumor of high grade malignancy.

TABLE 4. *Relation of symptoms to the grade of tumor*

		TRANSITIONAL CELL GRADES				SQUAMOUS	UNDIFF.	UNCLASS.	TOT.
		1	2	3	4				
Initial symptom	Dysuria	7	6	9	13	4	6	0	
	Painless hematuria	23	10	8	3	3	0	0	47
	Painful hematuria	8	4	8	8	3	4	1	36
Never developed	Dysuria	19	6	3	2	1	0	0	31
	Hematuria	4	1	1	7	1	4	0	18
	Neither	0		0	0	0	0	0	1
Not stated		0	2	0	1	1	1	0	5

TREATMENT

Though many of these tumors were treated by one method alone, most, at one time or another had several types of treatment. The small, well localized tumors were treated almost entirely by endoscopic fulguration alone. The larger and more malignant tumors were generally more aggressively treated with various forms of local extirpation and radiation. When the small, well localized tumors which had initially been treated by fulguration alone recurred in a more serious form, they were then treated more aggressively. Total cystectomies were not done in this series.

Endoscopic fulguration. Seventy-three of the tumors were treated by fulguration, but only 36 in this manner alone; complete follow-ups were obtained on only 26 of the latter. Twenty of the 26 were grades 1 and 2 transitional cell carcinomas: 14 of these 26 patients are still alive, but 13 of them had only grade

1 malignancies. Of the 12 who died, 3 died of carcinomatosis, 1 died postoperatively from perforation of the bladder, and 2 died of uremia, 1 died of intercurrent disease, and the cause of death was not known in 5. Of the 10 patients with incomplete follow-ups, 2 were terminal when last seen.

TABLE 5. *Treatment of carcinoma of the bladder by fulguration*

	TRANSITIONAL CELL GRADES				SQUAMOUS	UNDIFF.	TOTAL
	1	2	3	4			
Total no. cases	33	18	10	6	4	2	73
Fulguration alone	22	6	4	1	2	1	36
Av. known surv.	7 yr. 9 mo.	1 yr. 4 mo.	3 yr. 1 mo.	1 yr.	3 days	1 wk.	5 yr. 4 mo.
Dead	3	4	2	1	1	1	12
Cancer	1	0	0	1	0	1	3
Uremia	0	1	1	0	0	0	2
Intercur. dis.	0	1	0	0	0	0	1
Perf. bladder	0	0	0	0	1	0	1
Not known	2	2	1	0	0	0	5
Alive	13	0	1	0	0	0	14
Lost	6	2	1	0	1	0	10
Terminal when last seen	1	0	0	0	1	0	2

TABLE 6. *Open excision and fulguration of bladder carcinomas*

	TRANSITIONAL CELL GRADES				SQUAM.	UNDIFF.	TOTAL
	1	2	3	4			
Total no. cases	7	3	4	4	0	3	21
Av. survival (compl. fol. ups)	5 yr. 1 mo.	4 yr. 6 mo.	1 yr. 2 mo.	9 mo.		1 yr.	2 yr. 6 mo.
Dead	3	2	4	4	—	1	14
Cancer	0	1	2	0	—	1	4
Sepsis	0	0	1	0	—	0	1
Not known	3	1	0	4	—	0	8
Alive	1	1	0	0	—	0	2
Lost	3	0	0	0	—	2	5
Terminal	0	0	0	0	—	0	0

Cystotomy with local excision and fulguration of the tumor. This procedure consisted of opening the bladder, excising the presenting portion of the tumor (not the entire thickness of the bladder wall) and cauterization of the base of the tumor. Cauterization was usually done with a fulgurating current but in a few instances a hot soldering iron was used. The lesions treated in this manner were considered too large to destroy endoscopically. Twenty-one patients were treated in this manner with an average survival of 2 years and 6 months for those with complete follow-ups. Only 2 patients are still alive and they were only grade 1 and 2 transitional cell tumors. Four died of carcinomatosis, 1 of sepsis and the cause of death was not known in 8.

PARTIAL CYSTECTOMY

Eight cases were treated by partial cystectomy. Most of these tumors were of a rather high grade of malignancy. This procedure was carried out only for tumors located on the dome and anterior wall of the bladder where they were more accessible for excision. The one exception was a tumor located on the neck and anterior wall of the bladder. In this case an unsuccessful anastomosis between the bladder and urethra was attempted and a permanent vesicovaginal fistula resulted. Complete follow-ups were obtained on only 4 patients with an average survival of 3 years and 3 months. Of the 3 known to be dead, only 1 was known to have died of carcinoma. The cause of death in 2 others was not known. The fourth case had a complete follow-up and is still alive and free of disease. Incidentally, this is the only cure of a squamous carcinoma in the entire series. The 4 patients with incomplete follow-ups were never heard from again after their initial hospital stay.

TABLE 7. *Partial cystectomy*

	TRANSITIONAL CELL GRADE				SQUAMOUS	UNDIFF.	TOTAL
	1	2	3	4			
No. cases	0	2	3	1	1	1	8
Av. survival (compl. fol. ups)	—	—	4 mo.	4 yr. 6 mo.	7 yr. 3 mo	3 mo.	3 yr. 3 mo.
Dead	—	—	1	1	0	1	3
Cancer	—	—	0	0	0	1	1
Cause unkn.	—	—	1	1	0	0	2
Alive	—	—	0	0	1	0	1
Lost	—	2	2	0	0	0	4

Radon seeds. Treatment consisted of implanting 8 to 20 radon seeds into and around the tumor spaced about 1 centimeter apart with the bladder distended. Usually, if the tumor protruded appreciably into the lumen of the bladder, the greater part of the tumor was either resected with a cutting current or destroyed by fulguration before implanting the radon seeds into its base. Twenty-five tumors were treated in this manner with an average patient survival of 3 years and 1 month for the 15 cases with complete follow-ups. The 2 patients still living had only grade 1 and 2 transitional cell carcinomas. Thirteen are known to be dead: 6 died of carcinoma, 1 of general x-ray reaction (the patient had deep x-ray therapy), 1 of intercurrent disease and 1 of perforation of the bladder incident to implantation of the radon seeds. In 2 cases, the cause of death was not known. Of the 10 cases with incomplete follow-up, 3 were terminal when last seen.

Deep x-ray therapy. Deep x-ray therapy was given via 2 or 4 portals in amounts varying from 1600 to 9000 r. u. It was used when it was believed that the tumor had not been completely destroyed by the previous treatment or when the lesion was considered initially inoperable. Thirty-two cases were treated in this manner: None are known to be still living and 23 are known to be dead. The average survival of the patients with complete follow-up was 1 year and 4 months. Eight of them are known to have died of carcinomatosis, 1 of general x-ray reaction, 2 of uremia, 1 of sepsis and 1 of coronary occlusion. The cause of death was not known in 10 cases. Of the 9 cases with incomplete follow-up, 3 were terminal when last seen.

TABLE 8 *Treatment of bladder carcinomas with radon seeds*

	TRANSITIONAL CELL GRADES				SQUAM.	UNDIFF.	TOTAL
	1	2	3	4			
Number cases	6	7	5	4	0	3	25
Av. survival (compl. fol. ups)	7 yr. 6 mo.	3 yr. 7 mo.	11 mo.	1 yr. 4 mo.	—	10 mo.	3 yr. 1 mo
Dead	3	2	3	3	—	2	13
Cancer	1	1	2	1	—	1	6
X-ray reaction	0	1	0	0	—	0	1
Uremia	0	0	0	1	—	1	2
Intercur. dis	0	0	1	0	—	0	1
Perf. bladder	1	0	0	0	—	0	1
Not known	1	0	0	1	—	0	2
Alive	1	1	0	0	—	0	2
Lost	2	4	2	1	—	1	10
Terminal	1	1	1	0	—	0	3

TABLE 9. *Treatment of bladder carcinoma by deep x-ray therapy*

	TRANSITIONAL CELL GRADES				SQUAMOUS	UNDIFF.	TOTAL
	1	2	3	4			
Number of cases	4	7	5	12	2	2	32
Av. survival (compl. fol. ups)	4 yr. 8 mo.	7 mo.	4 mo.	1 yr.	1 yr. 6 mo.	—	1 yr. 4 mo.
Dead	3	5	4	9	2	—	23
Cancer	1	1	1	3	2	—	8
X-ray reaction	0	1	0	0	0	—	1
Uremia	0	0	2	0	0	—	2
Sepsis	0	0	0	1	0	—	1
Intercur. dis	1	0	0	0	0	—	1
Not known	1	3	1	5	0	—	10
Alive	0	0	0	0	0	—	0
Lost	1	2	1	3	0	2	9
Terminal	0	1	0	2	0	0	3

Open x-ray. Open x-ray treatment was devised by D. K. Rose in 1934 and used in the treatment of far advanced cases which were considered to be otherwise hopeless. Only tumors on the floor and the adjacent lateral wall of the bladder were considered suitable for this therapy. The principle of this treatment was to apply a large, potentially cancer-lethal dosage of x-ray directly to the tumor-bearing surface of the bladder. The bladder was first opened and marsupialized in the operating room and the base of the bladder exposed. The surrounding tissue was protected by lead plates. The patient was then taken to the x-ray therapy room where the electrode was placed as close to the tumor as possible and 1500 to 7000 r. u. of x-ray given in 1 dose, the average being 6000 u. Only 6 received less than 4000 u.; 3 patients received 2 treatments each, about 2 months apart, the total dosage varying from 5500 to 10,060 r. u.

Thirty-four patients were treated in this manner; only 2 are still living and they are free of tumor. Both of these were grade 3 transitional cell carcinomas and quite large at the time of treatment. Thirty patients are known to be dead: 6 died of carcinomatosis, 2 of general x-ray reaction, 3 of gangrene of a loop of bowel from the local effect of the radiation with perforation and peritonitis, 2 of uremia, 1 of sepsis, 1 of intercurrent disease, and in the remaining 15 the cause of death was not known. All but 2 cases had complete follow-up, the average survival being 1 year and 5 months. Most of these tumors were of high grade malignancy, only 7 of the 34 were classified as grades 1 and 2 transitional cell carcinomas.

TABLE 10. *Open x-ray treatment of bladder carcinoma*

	TRANSITIONAL CELL GRADES				SQUAM.	UNDIFF.	TOTAL
	1	2	3	4			
Number of cases	2	5	11	9	5	2	34
Average survival (compl. fol. ups)	1 yr. 9 mo.	1 yr. 7 mo.	2 yr. 2 mo.	1 yr.	5 mo.	5 mo.	1 yr. 5 mo.
Dead	2	4	8	9	5	2	30
Cancer	0	0	1	2	2	1	6
X-ray reaction	0	1	1	0	0	0	2
Uremia	0	0	0	2	0	0	2
Sepsis	0	1	0	0	0	0	1
Intest. perf.	0	1	0	1	1	0	3
Intercour. dis.	0	0	0	1	0	0	1
Not known	2	1	6	3	2	1	15
Alive	0	0	2	0	0	0	2
Lost	0	1	1	0	0	0	2

Three of these cases had metastases at the time of the open x-ray treatment. The treatment was administered anyway in an attempt to relieve intractable dysuria. At autopsy no cancer was demonstrable in any of the bladders (7 cases).

SURVIVALS

Of the 135 patients, 83 are known to be dead and 21 alive (77 per cent). The average survival for the entire 104 patients was 2 years and 10 months with 29 (28 per cent) five year survivals. Of the 77 patients with definite malignancy (grade 1 tumors excluded because of questionable malignancy), the average survival was only 1 year and 7 months and there were only 7 (9 per cent) 5 year survivals. The average duration of symptoms before the patients entered the hospital was 3 years and 1 month and was approximately the same for all grades of malignancy. Thus the average length of life from the time of onset of symptoms until death was approximately 5 years and 11 months.

Grade 1 Transitional cell carcinoma. The grade 1 transitional cell carcinomas had, by far, the longest survivals in the entire series. It must be emphasized that this is a lesion of low grade malignancy and many pathologists still call them "papillomas." As a matter of fact, in 20 of the 38 tumors in this group there was considerable question microscopically whether the tumor was malignant at all, even by the most liberal standards. However, due to their tendency to recur and become more malignant, they were classified as carcinomas. Of the 27 with complete follow-up, the average survival was 6 years and 11 months and there were 22 five year survivals. Fifteen are still living with an average follow-up of 7 years and 11 months. Twelve are dead with an average survival of 5 years and 8 months. Eight of the 15 living patients are still free of tumor, 7 had recurrences when last seen. Of the 12 cases known to be dead, only 3 are known to have died of carcinoma of the bladder. One died of carcinoma of the larynx, 1 postoperatively, and 1 of coronary disease. The cause of death in 6 of the cases is not known.

Of the 11 cases with incomplete follow-up, 4 were free of tumor when last seen and 2 had recurrences (2 of the latter were terminal). Three patients were never heard from again after their initial hospital stay. The average follow-up for these lost cases was only 1 year and 11 months. One case was followed 13 years before being lost. It is interesting that 3 of the cases had distant metastases, making it likely that the tumors were actually of a higher grade of malignancy than their often very small biopsies indicated.

Grade 2 transitional cell carcinoma. Twenty-three (20.7 per cent) were grade 2 transitional cell carcinomas. Of the 15 patients (65.2 per cent) who had complete follow-up, the average survival was 2 years and 3 months, and there were 3 five year survivals. Two are still living with an average follow-up of 7 years and 9 months, although 1 had a recurrence when last seen. Of the 13 cases known to be dead, the average survival was only 1 year and 4 months. Six (46 per cent) died of carcinoma, 3 postoperatively, and 1 of heart disease. The cause of death was not known in 3. Eight cases (35 per cent) did not have complete follow-ups; they were followed for an average of 4 years, the longest follow-up being 17 years. Three were free of carcinoma, 1 had a small recurrence and 1 had terminal carcinoma when last seen. The remaining 3 cases were never seen again after the initial hospital treatment.

Grade 3 transitional cell carcinoma. Twenty-five (22.5 per cent) were grade 3 transitional cell carcinomas. Of the 21 patients (84 per cent) who had complete follow-up, the average survival was 1 year and 8 months and there were 3 five year survivals. All 3 of these patients are still living with an average follow-up of 6 years and 11 months. Two of these patients are still free of tumor and have had no recurrence since the initial treatment of the lesion. Of the 18 known to be dead, the average survival was only 10 months. Eight (44 per cent) died of carcinoma, 3 (17 per cent) postoperatively, and 1 died of other causes. The cause of death was not known in 6 cases. Of the 4 patients with incomplete follow-up, 2 had recurrences when last seen and 2 were not seen again after their initial hospital stay. The longest follow-up among the lost cases was 4 years and 8 months and the average follow-up was 1 year and 3 months.

Grade 4 transitional cell carcinoma. Twenty-five (22.5 per cent) were grade 4 transitional cell carcinomas. Twenty-one (88 per cent) had complete follow-ups with an average survival of 1 year and 1 month. None are still living and none survived five years. Thirteen (59 per cent) died of carcinoma, 1 died of causes not related to the bladder lesion and 2 died postoperatively. The cause of death was known in 6 cases. Three of the patients had incomplete follow-ups with an average follow-up of only 1 week; 2 of these were in a terminal condition when last seen.

TABLE 11. *Relationship of the grade and prognosis of carcinoma of the bladder*

GRADE OF TUMOR	NO CASES	NO DEAD	AVERAGE SURVIVAL	NO. ALIVE	AVERAGE FOL UP	NO. LOST	AVERAGE FOL. UP	TERMINAL	5 YR. SURV.	ADDITIONAL 5 YR. SURV. (LOST CASES)
1	38	12	5 yr. 8 mo.	15	7 yr. 11 mo.	11	1 yr. 11 mo.	3	22	1
2	23	13	1 yr. 4 mo.	2	7 yr 9 mo.	8	4 yr. 0 mo.	1	3	3
3	25	18	10 mo	3	6 yr. 11 mo.	4	1 yr. 3 mo.	0	3	0
4	25	22	1 yr. 1 mo.	0		3	1 week	2	0	0
Squam.	12	10	7 mo.	1	7 yr. 3 mo.	1	None	1	1	0
Undiff.	11	8	6 mo.	0	. .	3	None	0	0	0
Unclass.	1	1	2 mo.	0		0		0	0	0
Total	135	83	1 yr. 7 mo.	21	7 yr. 8 mo.	30	1 yr. 7 mo.	7	29	4

Squamous carcinoma. Twelve (11.5 per cent) were primarily squamous carcinomas. Eleven had complete follow-up with an average survival of 1 year and 2 months. The only 5 year survival is still alive and free of carcinoma after 7 years and 3 months. The remaining 10 patients are known to be dead with an average survival of only 7 months. Only 1 patient had an incomplete follow-up, was far advanced when first seen, refused an open operation, and was never heard from again. Two other patients who initially had transitional cell carcinoma later developed squamous carcinoma. This occurred in 1 case 3 years after the diagnosis of transitional cell carcinoma was made, and the patient died 2 months later of carcinomatosis. The other occurred 17 years later, and after a partial cystectomy was done, was not heard of again.

Undifferentiated carcinoma. Eleven (10.6 per cent) of the tumors were undifferentiated carcinomas. Only 8 patients (72.7 per cent) had complete follow-up and all of these are known to be dead within 5 years. The average survival for the 8 patients with complete follow-up was only 6 months. Of the 3 without follow-up, none was seen again after the initial hospital stay.

Lymphatic vessel and vein invasion. In the entire series (135 cases), 11 specimens showed tumor in the lymphatic vessels (there were probably more but the small size of the biopsies made it impossible to study this feature of the tumor). One of these patients had a partial cystectomy with a cure, but the remaining 10 had an average survival of only 3 months. Only 2 specimens showed conclusive evidence of vein invasion. Both of these patients were dead within 3 months.

Prostatic invasion. The prostate was found to be invaded in only 2 cases and this was found only at autopsy.

The present status of the cases of this series is:

- Alive: 21 (15 grade 1 transitional cell carcinomas)
  - 14 are still free of tumor
  - 7 had recurrences when last seen
- Dead: 83
  - 39 are known to have died of carcinoma
  - 1 died of carcinoma of the larynx
  - 3 died of other diseases but were free of carcinoma at autopsy
  - 1 died of other diseases but still had carcinoma of the bladder at autopsy
  - 14 died postoperatively
  - 25 died of unknown causes
- Lost: 31
  - 7 were free of carcinoma when last seen
  - 4 had recurrences when last seen but the tumor was still apparently under under control
  - 7 had extensive carcinoma of the bladder when last seen and were considered terminal
  - 11 were not seen again after their initial hospital stay

AUTOPSIES

Only 7 ($\frac{1}{3}$) of the autopsied cases had metastases (table 12). Three cases without metastases had tumor infiltration into the perivesical soft tissue. The remaining 11 were apparently operable in that removal of the entire bladder, prostate and seminal vesicles would have removed all of the tumor. Of the 10 patients who died of renal complications (uremia and pyelonephritis), only 2 had cancer outside the bladder. Only 4 died of carcinomatosis. Five of the deaths were directly attributable to the treatment (general x-ray reaction, local x-ray effect with necrosis and perforation of the bowel and bladder). Certainly the upper urinary complications and the therapeutic measures employed were responsible for more of the deaths than the carcinoma per se.

DISCUSSION

The pathologic pictures of carcinoma of the bladder is often misleading. Many of these tumors have areas of varying degrees of malignancy in a single specimen. The tumor, of course, is no less malignant than its most malignant part and consequently the need for adequate biopsies cannot be stressed too greatly. The most superficial part of the tumor is usually the most benign area. Also, different areas on the surface of a lesion will sometimes be of different grades of malignancy (Albarran). With small biopsies the most malignant portion of the tumor is frequently missed. This is borne out by the fact that three of the apparently benign grade 1 transitional cell carcinomas developed distant metastases. It was even better illustrated by Dean who found that when the entire

TABLE 12. *Autopsies*

AUTOPSY NUMBER	GRADE OF TUMOR	CAUSE OF DEATH	LOCAL EXTENSION TO	METASTASIS	OBSTR. URETER	INFECT. KIDNEY	TREATMENT
1. 6898	Trans. ca. grade 2	Uremia	Semi. vesicles, prostate, lymph vessels	None	Bilat.	Bilat.	Fulguration
2. 11334	Ditto	Arterial thrombosis with embolism	None	None	None	None	Fulguration
3. 8617	Ditto	Gen. x-ray reaction	None	None	Bilat.	Left	Radon seeds Open x-ray (6600 r.u.) Deep x-ray (3150 r.u.)
4. Done at City Hosp.	Ditto	Carcinomatosis	Vesico-vag., septum, abd. wall and skin (thru cystostomy opening)	Liver, lungs, femur, iliac and aorta nodes	Bilat.	Suppurative, bilat.	Fulguration
5. 4753	Trans. ca. grade 3	Uremia	None	None	Bilat.	Bilat.	Fulguration
6. 3747	Ditto	Not known	Perivesical soft tissue	Not known	Not known	Not known	Cystotomy with local excision and fulg. of the base
7. 6706	Ditto	Uremia and gen. x-ray reaction	None	None	Left	Left	Fulguration Open x-ray (5000 r.u.) Deep x-ray (1600 r.u.)
8. 7273	Ditto	Sepsis (post-op. pyonephrosis)	None	None	Bilat. (anomaly with only 1 ureter)	Bilat. pyonephrosis	Cystotomy with local excision and fulg. of tumor base
9. 10496	Ditto	Uremia	Perivesical soft tissue	None	Bilat.	None	Deep x-ray (4800 r.u.) Fulguration

10. 6599	Trans. ca. grade 4	Sepsis	None	None	Bilat.	Bilat.	Deep x-ray (2400 r.u.) Fulguration
11. 8306	Ditto	Carcinomatosis	Prostate, ureter, left rectum, perivesical, soft tissue, peritoneum	Liver, peribronchial, supraclavicular axillary, aortic & ing. nodes	Bilat.	Left	Fulguration
12. 7348	Ditto	Coronary occlusion	None	Iliac and aortic nodes	Left	None	Open x-ray (6500 r.u.)
13. 11349	Trans. ca. grade 4	Carcinomatosis	Prostate, rectum, ureters	Iliac, aortic, retroperitoneal, supraclavicular, inguinal & hepatic nodes	None	Right	Open x-ray (3000 r.u.)
14. 7212	Trans. ca. grade 4	Peritonitis due to perf. of gut by x-ray necrosis	None	None	None	None	Open x-ray (3000 r.u.)
15. 8570	Ditto	Uremia	Prostate, urethra	Iliac nodes	Bilat.	None	Open x-ray (6500 r.u.)
16. 6924	Undiff. ca.	Uremia	None	None	Left	Right	Fulguration & open x-ray (4000 and 5000 r.u.)
17. 4466	Ditto	Uremia	Perivesical soft tis.	None	Bilat.	None	Radon seeds (10)
18. 6973	Squamous	Uremia	Prostate, pubis, perivesical soft tis.	Liver	Bilat.	Bilat.	Deep x-ray (6400 r.u.)
19. 10148	Ditto	Carcinomatosis	Perivesical, soft tis., pubis, ant. abd. wall, scrotum	Ing., iliac, aortic, peribronchial, mesenteric and mediastinal nodes, lung & pleura	Bilat.	None	Deep x-ray (1600 r.u.)
20. 2508	Ditto	Peritonitis due to x-ray gangrene of bowel	None	None	Left	Left	Open x-ray (6000 r.u.)
21. 7906	Ditto	Perf. of bladder by fulguration	None	None	Bilat.	Bilat.	Fulguration (endoscopically)

thickness of the bladder wall was sectioned (cystectomy cases) the degree of malignancy was greater than the preoperative biopsy in over one half of the cases. However, it is frequently impossible to differentiate these tumors grossly or microscopically as benign or malignant because so many of them are multiple, tend to recur repeatedly in different areas of the bladder, and tend to become definitely malignant with recurrence. Because of these factors, many tumors thought initially to be benign microscopically are probably malignant. The recent work of Hovenanian and Deming in which a "papilloma" of the bladder was transplanted successfully to the anterior chamber of the eye of a guinea pig is further evidence of their malignancy. These tumors, though they rarely metastasize, usually cause death by blockage of the upper urinary tract with resulting uremia and pyelonephritis.

In view of the fact that squamous metaplasia was frequently present in addition to multiple tumors, it would seem that the lesion is not a local one but that large areas or even the entire bladder mucosa is potentially malignant or precancerous. In order to cure this type of lesion it would be necessary to remove the entire bladder mucosa and nothing less than a total cystectomy would be adequate. The main objection to this procedure in the past has been the high operative mortality and the postoperative obstruction and infection of the upper urinary tract which takes place. Recently 27 patients have had total cystectomies using the Cordonnier technique without an operative mortality. Only 1 patient showed any appreciable increase in hydronephrosis following operation and only 5 have had symptoms of pyelonephritis. It seems likely that the Cordonnier technique will eliminate most of the objections to total cystectomy for carcinoma of the bladder and thus permit more cures. The fact that only one third of the autopsy specimens revealed carcinoma beyond the bladder indicates that a number of the patients could have been cured had the bladder been successfully removed. In dealing with these patients who have such a poor prognosis and high degree of morbidity, there is certainly very little to be lost in giving radical treatment.

TABLE 13. *End results in carcinoma of the bladder*

	NO CASES	5 YR SURV	APPARENT CURES	AVERAGE SURVIVAL	AVERAGE SURVIVAL*	5 YR. SURVIVAL*
		per cent	*per cent*			*per cent*
Barnes Hospital	135	28	13.3	2 yr. 10 mo.	1 yr. 7 mo.	9
Memorial Hospital (Marshall)	316	—	6.0*	—	2 yr.	17
Mayo Clinic (Counseller and Walters	600	28	—	—	—	—
Bladder Tumor Registry	902	33.24	—	—	—	—

* Grade 1 transitional cell carcinomas not included.

In reporting cases of carcinoma of the bladder, it is very important to indicate the grade of malignancy of the tumors, for most likely the results of treatment will be closely related to the percentage of grade 1 transitional cell carcinomas included in the series (table 13).

SUMMARY

One hundred and thirty-five consecutive cases were studied. All tumors were graded microscopically. Thirty-eight were grade 1 transitional cell carcinomas, 23 were grade 2, 25 were grade 3 and 25 were grade 4. Eleven were undifferentiated and 12 were primarily squamous carcinomas. One was listed as an unclassified carcinoma. Although the gross appearance of a tumor is usually indicative of its degree of malignancy, there are many which appear benign grossly but are, in reality, quite malignant and vice versa. Although the size of the tumor is not significantly related to its degree of malignancy, the patients with the larger ones, as a group, have a much poorer prognosis than those with the smaller tumors. Seventy-five per cent of the transitional cell and undifferentiated carcinomas were located on the floor of the bladder. Over one-half of the squamous carcinomas were located on the dome and anterior surface of the bladder. One half (3 out of 6) of the tumors involving virtually the entire bladder surface were only grade 1 transitional cell carcinomas. The prognosis of tumors on the dome and anterior wall of the bladder is much worse than that of those on the base. The ages of the patients when first seen ranged from 39 to 82 years with an average of 60.8 years. Ninety four were males and 41 females.

Painless hematuria was usually associated with tumors of low grade malignancy, whereas dysuria was usually associated with tumors of high grade malignancy. One hundred and four (77 per cent) of the patients had complete follow-ups. The average survival for all patients with complete follow-ups was 2 years and 10 months and 28 per cent had 5 year survivals. Twenty-one patients are still known to be alive but 15 of these were only grade 1 malignancy. Treatment in general was satisfactory for tumors of low grade malignancy and was generally unsatisfactory for those of high grade malignancy regardless of the form of treatment used. There were no cures or 5 year survivals in the group treated by closed (deep) x-ray. There were 2 cures in the group which had open x-ray therapy. No total cystectomies were done.

CONCLUSIONS

Biopsies of bladder tumors should be as generous in size and depth as possible in order to obtain a better idea of the nature of the lesion being treated.

Treatment of the grade 1 and some of the small, well localized grade 2 transitional cell carcinomas has been fairly satisfactory using conservative methods. Treatment of tumors of a higher grade of malignancy by conservative methods, however, has been unsatisfactory and a more radical approach adopted.

In evaluating results of treatment in a series of cases of carcinoma of the bladder it is very important to know how many grade 1 transitional cell carcinomas are included. The series containing the larger percentage of these tumors should have proportionally longer survivals.

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REFERENCES

Albarran, J.: Les tumeurs de la vessie. Paris: G. Steinheil, 1891.

Ash, E. J.: Epithelial tumors of the bladder. J. Urol., 44: 135, 1940.

Barringer, B. S.: Five year control of bladder cancers by radon implants. J.A.M.A., 120: 909, 1942.

Colston, J. A. C. and Leadbetter, W. F.: Infiltrating carcinoma of the bladder. J. Urol., 36: 669, 1936.

Committee on Cancer Registry: Cancer of the bladder. J. Urol., 31: 423, 1934.

Cordonnier, J. J.: Ureterosigmoid anastomosis. Surg., Gynec. & Obst., 88: 441, 1949.

Counseller, V. S. and Walters, W.: Malignant tumors of the bladder. Surg., Gynec. & Obst., 56: 448, 1933.

Dean, A. L.: Comparison of the malignancy of bladder tumors as shown by the cystoscopic biopsy and subsequent examination of the entire excised organ. J. Urol., 59: 193, 1948.

Hovenanian, M. D. and Deming, C. L.: Heterologous transplantation of uroepithelial tumors. Part II Transplantation of bladder tumors. Yale J. Biol. and Med., 19: 149, 1946.

Jewett, H. J. and Strong, G. H.: Infiltrating carcinoma of the bladder. J. Urol., 55: 366, 1946.

Kretschmer, H. L.: Hematuria: A clinical study based on 933 consecutive cases. Surg., Gynec. & Obst., 40: 683, 1925.

Keyes, E. L.: Epithelial bladder tumors attacked by radon and fulguration. J. Urol., 59: 875, 1948.

Marshall, V. F.: Transplantation of the ureters and total cystectomy. J. Urol., 58: 244, 1947.

Rabson, S. M.: Leukoplakia and carcinoma of the bladder. J. Urol., 35: 321, 1936.

Rose, D. K.: Open x-ray therapy in carcinoma of bladder. J. Urol., 55: 267, 1946.

Spooner, A. D.: Metastasis in epithelioma of the urinary bladder. Tr. Am. Assn. Genito-Urin. Surg., 27: 81, 1934.

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MUCOID ADENOCARCINOMA OF THE URACHUS INVADING BLADDER

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Carcinoma of the urachus is a rare disease. Hayes and Segal, after reviewing the literature, reported 45 cases in 1945, including 1 of their own. In 1946, Higgins reported 2 cases, and Rappoport and Nixon another in a 26 year old man. Cawker added 1 case and Prentiss 3 more in 1947.

We wish to add 2 cases to this series, bringing the total reported to date to 54.

CASE REPORTS

Case. 1 W. L., a 63 year old white man, was referred to S. P. H. by H. H. O. on December 26, 1947 because of gross hematuria. The patient stated that blood had been present in his urine daily for the past 2 to 3 months, but he remembered passing blood as far back as 3 years ago. He also had nocturia every hour accompanied by burning. Past medical history and a review of symptoms by systems was negative except for recent shortness of breath. There was no weight loss.

Examination of the head, neck and chest was negative except for marked pallor of buccal mucosa and lips. The blood pressure was 140/70. The abdomen was negative except for a large right, indirect inguinal hernia which descended into the scrotum. The prostate gland was benign and enlarged to grade 1 plus. The voided urine was grossly bloody, contained many pus cells and small pieces of tissue.

Cystoscopy revealed the bladder capacity to be markedly reduced. An infiltrating, sessile tumor covered with sloughing tissue, about 3 to 4 cm. in diameter was seen on the right lateral, anterior bladder wall and dome. The remaining bladder mucosa was inflamed. Plain x-rays, excretory urograms and cystograms were essentially normal and not revealing. The patient was hospitalized on January 2, 1948. The red blood count was 2,070,000, hemoglobin 4 gm., white blood count 11,400. The differential was normal. The urine was grossly bloody. The blood nonprotein nitrogen was 36.6 mg. per cent and the blood sugar was 115 mg. per cent. Urine culture revealed Staph. albus. X-rays of the chest, spine and pelvis showed no metastases.

During the following 12 days, the patient received 9 pints of blood. A biopsy taken from the tumor with the cutting loop proved to be carcinoma. The bladder capacity was considerably increased and there was a greater area of normal mucosa present. A segmental resection of the bladder was planned.

Surgery was performed on January 13, 1948 (S. P. H.). The bladder was found to be the seat of an extensive infiltrating penetrating carcinoma which resembled a fibroid uterus in size and consistency. The entire anterior wall, dome and right lateral wall of the bladder were involved by tumor. The peritoneal reflection over the dome of the bladder was indurated and densely adherent to the tumor.

Intra-abdominally, there was no evidence of metastasis to the hypogastric or iliac lymph nodes by palpation. A total prostatocystectomy with cutaneous ureterostomies was decided upon in view of the fact that the bowel was not prepared. In isolating the right ureter, many adhesions had to be freed. When the ureter was finally freed and cut, the proper length could not be obtained for cutaneous ureterostomy. There did not appear to be any choice than to implant the ureter into the sigmoid, after the method of Coffey. The left ureter could not be found and therefore it was decided to tie the latter off at the juxtavesical junction at the time of cystectomy and sacrifice the left kidney, in order to conserve time.

Prior to closing the peritoneum, the portion adherent to the dome was circumcised and left adherent to the tumor. The healthy peritoneum was then closed. The bladder, seminal vesicles, and prostate were extirpated in toto. The left ureter was doubly ligated with chromic catgut. The space of Retzius was drained and the wound closed in the usual manner.

The gross specimen consisted of a bladder, prostate and seminal vesicles removed in toto, and measured 7 cm. transversely and 11 cm. long. The posterior wall of the bladder was partly covered by peritoneum. The dome of the bladder was involved by a papillary gelatinous growth, which ended rather abruptly at the trigonum. The surface of the tumor was necrotic. Present within the pelvic fat tissue were numerous gelatinous-appearing nodules ranging in size up to 3 mm. (One biopsy had been obtained on January 7, 1948 and sections showed carcinoma.)

Microscopic examination of sections from the dome of the bladder showed the surface to be covered by a regular transitional epithelium. The wall in extensive areas was penetrated by a richly mucus producing tumor. Glandular spaces were lined by tall, mucus secreting, columnar epithelial cells which in many areas had been shed and were enmeshed within the mucoid material in the form of the so-called "Siegel-ring" cells. The growth was identical with the one observed in the previous biopsy. Sections from the neck of the bladder did not show malignant involvement. Likewise the prostate was free from tumor. There was marked glandular hyperplasia. Sections from the seminal vesicles were pathologically negative. Sections from the regional lymph nodes, however, showed almost complete destruction of the lymphoid tissue and replacement. Small areas of lymphoid tissue were preserved at the center of the node, thus illustrating the "cobra" style invasion of the lymphnodes. Diagnosis: 1) urachal carcinoma of dome of urinary bladder with metastasis to regional lymph nodes; 2) glandular hyperplasia of prostate. See figure 1.

The postoperative course was complicated by "serous drainage" from the lower angle of the incision. This was noted on the eighth postoperative day. Three days later the patient coughed and eviscerated through the upper two thirds of his incision. He was taken to the operating room and closed with through-and-through interrupted tension sutures. The serous drainage continued from the lower angle of the wound in large amounts. The drainage was proven to be urine by indigo carmine injected intravenously, and excretory urograms. On

February 2, 1948 a left nephrectomy was performed. The drainage ceased at once and the remainder of the convalescence was uneventful. The patient was discharged from the hospital on February 13, 1948 on the thirtieth postoperative day. He received a total of 18 pints of whole blood during the entire hospital stay.

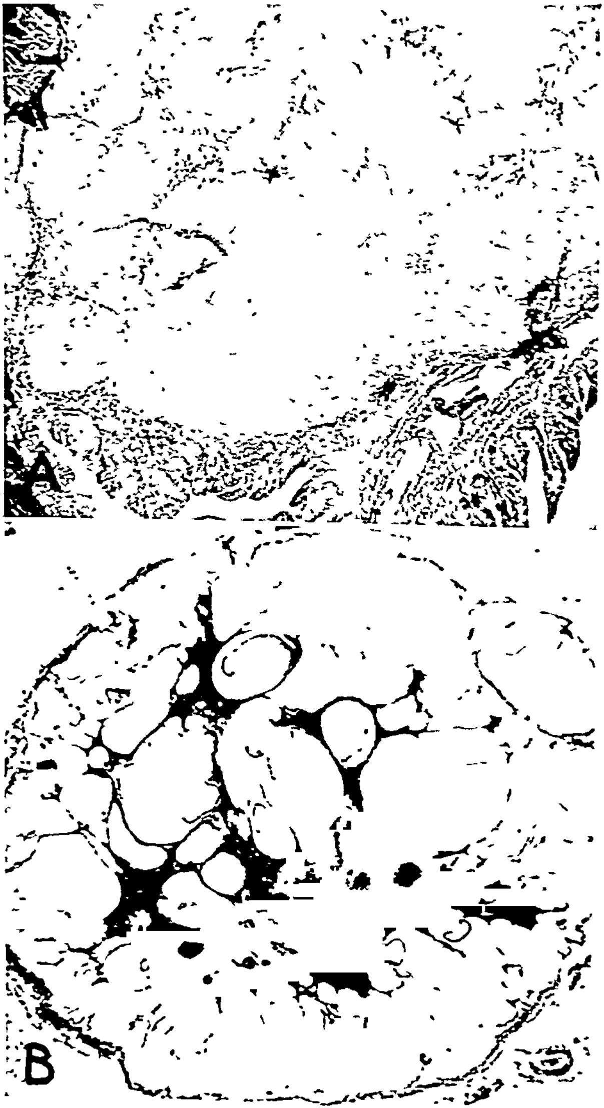

Fig 1 Case 1 *A*, invasion of muscularis of bladder by mucus producing tumor. *B*, lymph node Almost complete destruction of lymphoid tissue and replacement by tumor.

Twenty-two months postoperative, the patient offered no complaints. He had gained over 30 pounds in weight, and was enjoying a normal existence. His rectal urinations occurred approximately every 4 hours and were relatively free from fecal material. He had normal formed stools daily.

Case 2. H. K., a 46 year old white man, was seen by E. B. J. on May 10, 1947 complaining of dysuria accompanying a frequency of every $\frac{1}{2}$ to 1 hour, day and night. He noted terminal hematuria and at times the entire voiding was bloody. He further complained of pain in the right leg extending to the knee. His symptoms were present for 8 to 9 months. He had been treated for cystitis elsewhere. Cystoscopy revealed a circumscribed ulcerating area about 2 cm. in diameter in the anterior aspect of the fundus of the bladder. Urine contained pus and mucinous debris. X-rays of the chest and long bones were negative.

Surgery was performed on June 4, 1947 by E. B. J. A sausage-like mass was found attached to the summit of the bladder terminating in a solid thread-like cord extending up to the umbilicus. The peritoneal cavity was opened and explored for extension of the tumor and glandular involvement. No tumor implants or metastasis were found. The peritoneum was not adherent to the tumor. The bladder was opened and the tumor resected with a collar of normal bladder wall including all layers. The resultant defect was closed around a Pezzer catheter and the wound closed with drainage of the prevesical space.

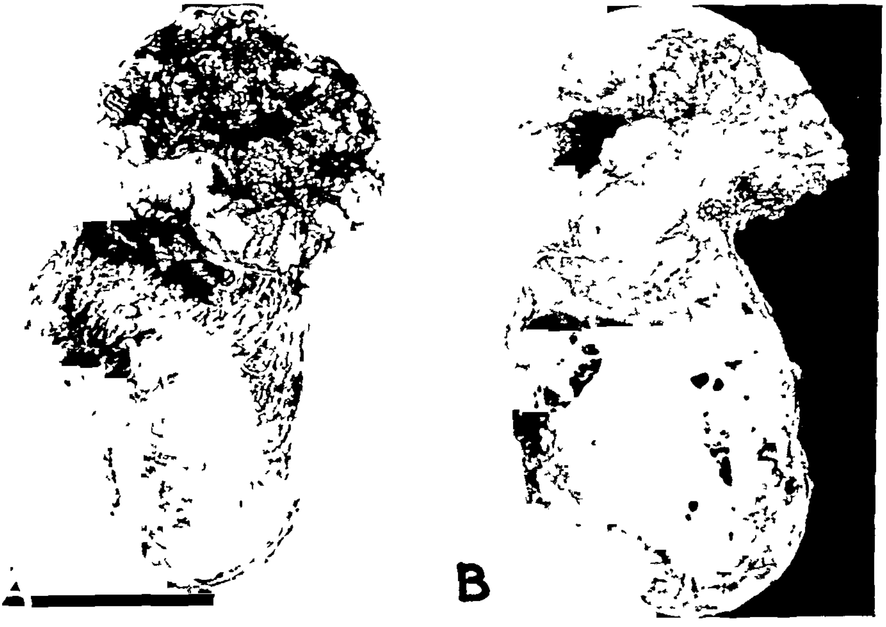

Fig 2 Case 2 *A*, surgical specimen Tumor with collar of normal bladder wall *B*, gross specimen opened Mucoid structure almost completely filling tumor

The gross specimen was 9 cm. long and had a transverse diameter in its mid area of 4 cm. and was roughly oval (fig. 2). It consisted of two parts: a proximal smooth surfaced, pseudocystic area about 5.5 cm. in its maximum diameter. The external surface of this mushroom-like, papillary, cauliflower-like tumor structure, apparently contained a considerable amount of colloid-like material. This tissue had been artificially perforated in the course of surgery. It connected with the proximal mass by an isthmus. The latter had its extreme upper pole and slender cord-like structure identified by a ligature which seemed to have been a point of attachment. Longitudinal section disclosed that the tumor area maintained the same papillary colloid structure but seemed to stop, so far as any gross identification was concerned, abruptly at the isthmus. The remainder of the specimen was filled with a slightly hemorrhagic, rich mucoid structure which completely filled the specimen and was surrounded at its periphery by a zone of tissue resembling keratin, almost 1 cm. thick. The tumor and its demarcation from the proximal portion of the specimen may be misleading, for the colloid material in the center of the specimen may actually be an extension of the tumor changing its character because of the limitations of the cyst wall.

Microscopic examination of sections from the dome of the urinary bladder showed the latter to be lined in some places with a regular transitional epithelium. In most areas, however, the latter was destroyed and replaced by an atypical glandular tumor which was characterized by masses of confluent adenomatous structures, most of which are widely distended and contained a mucoid material. They were lined by several layers of irregular, columnar, mucus secreting epithelium. The grossly described mushroom-like lesion showed the same type of neoplastic structure. Its surface was lined by a single layer of the same type of atypical goblet cells which obviously have given rise to this tumor. Its wall was thin and consisted of dense connective tissue. Diagnosis: 1) urachal carcinoma of dome or urinary bladder; 2) persistent urachus with urachal cyst.

The Pezzer catheter was removed on the eighth postoperative day and normal urination was experienced the following day. Convalescence was uneventful and the patient was dismissed from the hospital, apparently fully recovered, on the eleventh postoperative day. A course of radiation therapy was administered during the following month. The leg pains recurred and required opiates for relief. There were no urinary symptoms.

On December 10, 1947 the patient was re-admitted to the hospital for relief of pain in the right leg. There were no urinary symptoms and the urine specimen showed a slight trace of albumin and an occasional red blood cell and white blood cell. X-ray studies revealed multiple metastatic nodules in both lung fields. A soft tissue mass was found in the right side of the pelvic inlet extending beyond the margin of the sacrum. No bone metastasis was found. Excretory urograms were normal and the bladder contour was normal.

A paravertebral block, dorsal 2 and lumbar 1 and 2, was performed on December 12, 1947 resulting in complete relief of pain in the right leg. The leg pains recurred and a cordotomy was performed on January 12, 1948 with a permanent lasting relief of pain. Urinary retention was present postoperatively, requiring continuous catheter drainage. The patient was dismissed ambulatory with normal urinary function on February 7, 1948.

He was rehospitalized on April 7, 1948 with severe pain in the left leg. X-ray studies showed progression of the metastatic lesions. The pelvic mass was encroaching on the bladder, producing a deformity in the cystograms. The urine showed definite bladder infection. A cordotomy was performed on April 8, 1948 with a resultant relief of pain in the left leg. Convalescence was complicated by urinary retention and cystitis. Partial return to normal urination occurred but the cystitis persisted. The patient was dismissed from the hospital free from pain, and able to walk with some support, on May 29, 1948. He became progressively weaker, lost weight and expired 5 months later. No autopsy could be obtained.

Carcinoma of the urachus has been reported only during adult life. It occurs earlier than primary carcinoma of the bladder, and is borne out by the following reported age groups: third decade, 3 cases; fourth decade, 9 cases; fifth decade, 15 cases; sixth decade, 13 cases; seventh decade, 10 cases; eighth decade, none; ninth decade, 1 case.The youngest patient was 26 and the oldest 82. Eighty per cent of the lesions occurred in males.

Signs and symptoms usually occur late, since hematuria or masses are the first findings. Secondary infection or abdominal discomfort may cause the patient to seek medical attention, but the underlying lesion can be easily overlooked if a thorough examination is not performed. The passage of mucus and necrotic pieces of tissue in the urine is not an uncommon finding. Of all the cases reported, only one was discovered before the carcinoma had broken through the vesical mucosa.

Sessile necrotic, papillomatous, or mucus producing tumors arising from the dome of the bladder should be suspected of being urachal carcinomas which have invaded the bladder. Higgins states that pressure upon the abdomen during cystoscopy may force mucus or blood or both through the opening into the bladder. He was able to make a clinical diagnosis of mucoid carcinoma of the urachus in one of his cases by this method. Transurethral biopsy should confirm the preoperative diagnosis. If one is not aware of this lesion, it might be mistaken for a carcinoma of the bowel which has invaded the bladder.

Transurethral or suprapubic fulguration appears to be useless since the depth of the lesion cannot be ascertained, and may extend to the umbilicus. The lesion is highly resistant to x-ray therapy. The best results have been obtained with radical open surgery and should include peritoneum, perivesical fat and lymphnodes if possible. Total prostatocystectomy and transplantation of the ureters may be necessary, depending upon the extent of the lesion. Cystoscopic appearance of the lesion is very deceiving and therefore bimanual palpation may contribute much to the determination of its size and extent. Since most of the knowledge obtained is at the time of surgery, it would be wise to prepare the bowel prior in case total prostatocystectomy and ureterosigmoid anastomosis are decided upon at the time of surgery. Distal metastases occur late.

SUMMARY

Two cases of urachal carcinoma invading the bladder have been reported, bringing the total to date to 54.

The lesion is not common but should be borne in mind when carcinomas on the dome of the bladder are seen.

Radical surgery will elicit a higher percentage of cures.

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REFERENCES

Cawker, A. C.: Canad. Med. Assoc. J., 57: 586, 1947.
Hayes, J. J. and Segal, A. D.: J. Urol., 53: 659, 1945.
Higgins, C. C.: Urol. & Cutan. Rev., 50: 4, 1946.
Prentiss, R. J.: Calif. Med., 67: 000, 1947.
Rappoport, A. E. and Nixon, C. E.: Arch. Path., 41: 388, 1946.

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POSTOPERATIVE URINARY INCONTINENCE

EDWIN DAVIS

> "It is . . . cowardly to blink facts because they are not to our taste."
>
> —*John Tyndall*

It is my purpose to direct attention to an apparently simple explanation of at least some cases of transient difficulty in urinary control not infrequently observed following surgical removal of obstructing prostatic tissue, by whatever route. Incontinence of the type under consideration, tending toward spontaneous recovery during a period of several days to several weeks, is by no means necessarily the result of surgical incompetence, and in fact may complicate convalescence following flawless surgical technique.

Other than to mention that this discussion does not include faulty urinary control associated with the various forms of hypotonic and hypertonic neurogenic dysfunction, I propose to avoid entangling those present, as well as myself, in a dissertation upon the intricacies of the neuromuscular mechanism of urination. For the purpose of practical discussion let it suffice merely that we recognize that normally there exists a set of muscles, generally referred to as the external sphincter, located distal to the apex of the prostate, which serves effectually to maintain urinary continence even after complete ablation of prostate and bladder neck. Neurogenic dysfunction due to such central nervous system lesions as tabes, cord trauma or tumor, infections, multiple sclerosis and syringomyelia may be diagnosed before operation by cystometrographic and neurologic studies and those concerned be thus forewarned. There is obviously no reason why mechanical prostatic obstruction and degenerative central nervous system lesions should not coexist.

Although noted only occasionally, and rarely long-lasting or of serious consequence, unless complicated by undiagnosed neurogenic dysfunction, this disturbing and annoying interlude, marring an otherwise smooth convalescence, following either suprapubic, perineal or transurethral surgery, is of sufficiently frequent occurrence to merit thoughtful consideration as to cause and care. A review of the recent literature, however, indicates what may be interpreted only as almost total disinterest, or unwillingness to face the problem. It is perhaps irrelevant but nevertheless amazing to note that among 332 titles upon the subject of urinary incontinence listed in the Quarterly Cumulative Index during the decade ending July 1, 1947, only three deal with postoperative urinary incontinence, and 140 with enuresis! These three, however, are well worth reviewing.

SPHINCTER INJURY

The following quotation from Goodfellow[1] to whom Hugh Young[2] gives "credit for being the first* to make a success of (perineal) prostatectomy," enables one readily to understand why perineal prostatectomy entered upon its career in disrepute:

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[1] Goodfellow, G.: Median perineal prostatectomy. J. A. M. A., 43: 194, 1904.

[2] Keen, W. W. and DaCosta, J. C.: Surgery. Philadelphia: W. B. Saunders Co., 4: 438, 1908.

* Hamer, in his presidential address before the American Urological Association in 1929, stated: "The published record indicates that median perineal prostatectomy was first

"A median incision from the base of the scrotum to the margin of the anus is made, and carried to the membranous urethra, which is entered with a straight lithotomy knife and the opening extended into the bladder. The finger is then introduced into the bladder . . . and the enucleation . . . carried on, the time consumed for complete enucleation rarely being over five or ten minutes." Since this blind technique, as generally practiced in the '90s and after the turn of the century, with total disregard of perineal anatomy, inevitably involved stretching and tearing and in many instances irreparable damage to important structures and resulted in a high incidence of lasting incontinence and urethrorectal fistula, this stigma obviously was well deserved. Under these circumstances Keyes was not too far wrong in his pronouncement to the effect that whereas more suprapubic prostatectomy patients die, more perineal prostatectomy patients "wish they were dead."

The point, however, is that present day technique of perineal dissection based upon the principles laid down by Hugh Young[3] is such as to preclude any possibility of damage to external sphincter fibers. The same applies to the transurethral method, assuming both procedures in good hands and properly executed. And with respect to the suprapubic route it is difficult to understand how external sphincter damage could possibly occur even in the most incompetent hands. Yet the type of incontinence under consideration *does* occur occasionally following prostatic surgery, in the best hands, by way of any one of the three routes. At least this has been my own experience. The experience of others is for others to relate. The statement from the columns of the *Journal of the American Medical Association*[4] to the effect that "a slight degree of incontinence (resulting from injury to the external sphincter) is observed occasionally following removal of the prostate by any of the methods employed" may therefore be viewed as true and accurate with the exception of that portion within (my) parentheses. I believe that no informed individual would question the ability of the skilled urological surgeon to avoid the external sphincter fibers, by whatever route. Moreover, the same type of temporary incontinence may be observed following internal urethrotomy for the relief of chronic filiform stricture of the *anterior* urethra. Therefore, in that external sphincter damage is not the answer, it is obvious that we must look elsewhere.

NERVE INJURY

As to the question of possible surgical traumatic nerve injury, one would do well not to be too dogmatic lest one find himself (according to Ambrose Bierce's definition of the adjective "positive") "mistaken at the top of one's voice." Grant and Lich[5], with whom I agree that incontinence "follows on occasion the

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performed by Watson in 1889, Wishard in 1890, and Goodfellow in 1891. Each of these three operated without knowledge that it had been previously done."

[3] Young, H.: Conservative perineal prostatectomy. J. A. M. A., 41: 999, 1903.

[4] Queries and Minor Notes: J. A. M. A., 136: 1118, 1948.

[5] Grant, O. and Lich, R., Jr.: Consideration of the causes of incontinence, temporary and permanent, following perineal prostatectomy. J. Urol., 57: 61, 1947.

wake of the master as well as the novice," for "reasons imperfectly understood," suggest the possibility of lateral retractor pressure injury to the perineal nerve trunk which, during perineal dissection, "is readily palpable against the ramus" of the ischium. This is to be viewed as a valuable suggestion, and a thought to be borne in mind during each and every perineal dissection. Fagerstrom[6], basing his opinion upon reported cases (his own and others') of post-*suprapubic* prostatectomy incontinence and simultaneous development of diverticula of the *anterior* urethra, has suggested that these two phenomena may be "but two phases of a single neurogenic dysfunction," resulting from surgical injury to nerve pathways, rather than merely coincidental. I question whether our present limited knowledge justifies either the rejection or the unqualified acceptance of these and other plausible theories and opinions relating to the nerve injury etiology of post-prostatectomy incontinence. The following facts, however, seem pertinent.

Suprapubic prostatectomy, unless through deliberate intent or almost inconceivable incompetence, consists of a wholly intracapsular enucleation, leaving undisturbed the so-called prostatic capsule or posterior lobe or lamella of glandular tissue, as well as the true fibrous capsule.* It seems absurd to suppose that a suprapubic transvesical intracapsular approach to the prostate could result in injury to the nerve supply of the perineal musculature.

The same applies to the transurethral approach which in skilled hands is likewise an entirely intracapsular procedure.

The perineal approach to the prostatic capsule consists essentially of a subcutaneous dissection involving opening up the ischiorectal fossae, midline separation of the levator fibers and reflecting the rectal wall by blunt dissection, and requiring the scalpel only for the skin incision and for division of the central perineal tendon. This technique in good hands would seem to preclude the possibility of severence of important nerve fibers. After incision of the posterior prostatic capsule (or lamella), the perineal enucleation (like the suprapubic and transurethral) then also comes to be an entirely intracapsular procedure. Incidentally, the perineal enucleation is infravesical as well as intracapsular, by reason of which less vesical neck trauma is involved. During exposure, enucleation and closure care should be exercised to avoid retractor pressure upon the perineal nerve trunk. Also to be borne in mind is the possibility of suture injury to nerve fibers in the attempt toward too perfect restoration of the perineum during plastic closure. There being no hernia problem to contend with, requiring firm closure, it is difficult to conceive of nerve fiber injury resulting from mere restoration of prostatic capsule, bringing together the levator margins, reunion of the central tendon in the midline and loose approximation of subcutaneous tissues with 000 plain catgut.

Chronic preoperative pressure upon nerve trunks by the greatly enlarged prostate has been suggested as a factor which might explain some cases of poor urinary control, but for obvious reasons only relatively few. And therefore, since peripheral nerve damage is clearly not the entire answer, we must again look elsewhere.

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[6] Fagerstrom, D. P.: Etiology of acquired diverticula of the anterior urethra and its relation to the cause of post-prostatectomy incontinence. J. Urol., 49: 357, 1943.

* In fact, excepting the total or radical perineal procedures, the term "prostatectomy" is a misnomer, the operation actually consisting merely of an enucleation of obstructing prostatic lobes.

MUSCLE WEAKNESS OR ATROPHY OF DISUSE

All of which, by a process of elimination, brings us to a consideration of what seems to be an almost too simple explanation, based upon a well recognized physiological phenomenon which we may refer to as the atrophy of disuse. As everyone knows, a normal individual confined to bed for only a very few days will note general physical weakness upon arising. An arm in a sling or a leg in a cast rapidly loses strength and later becomes atrophic in degree as determined by duration of inactivity. In like manner, the obstructing prostate having served as a "stopper" for the vesical orifice for many months or even years, may be said to have assumed the duties of the external sphincter mechanism, thus preventing the escape of urine excepting upon voluntary effort. There then being no necessity for tonic contraction it is not unreasonable to assume that the resulting state of chronic relaxation existing over a period of weeks or months or even years will result in muscle weakness, and eventually in varying degrees of atrophy. Contrary to the belief expressed by Grant and Lich[5] it has been my observation and that of my associate, Dr. Lee, that the size of the prostate bears a definite relationship to the duration of the incontinence. This seems in keeping with the muscle atrophy theory, since the larger the prostate the longer its term of duty as a "stopper" in relieving the external sphincter, and also the more likely and the more extensive the damage to the internal sphincter. There is no question that age and general weakness and debility also exert a definite influence in retarding recovery of continence. In keeping with this statement is the relationship between effectiveness of sphincter control and general fatigue, as reported by patients describing late afternoon urinary difficulty as contrasted with forenoon perfection.

As stated by Fagerstrom,[6] "regardless of the route of surgical approach, the internal urinary sphincter is usually so severely incapacitated after prostatectomy that . . . its function may be wholly discounted." It is important, however, to point out that not infrequently dilatation and stretching of the internal sphincter by a large intravesical hypertrophy, over a preoperative period of months or years, has already damaged this structure beyond possibility of recuperation. Therefore, in many instances, it is the enlarging prostate itself which ruins one sphincter and relieves the other, thus incapacitating both, long before the arrival of the surgeon upon the scene.

The atrophy of disuse theory explaining temporary incontinence following prostatic surgery is justified by:

1) The occasional occurrence of this complication regardless of perfection of surgical technique, by any route.
2) Inadequate explanation upon basis of surgical trauma to sphincter fibers or nerve supply.
3) Direct relationship between general debility and duration of incontinence; also between size of gland and duration of incontinence.

4) Response to exercise treatment.
5) Relapse with general physical fatigue.
6) Occurrence of same type of incontinence following internal urethrotomy for stricture of anterior urethra.
7) Lack of any other plausible explanation.

PREVENTION

I am aware of no assured method of prevention of this troublesome interlude. There is no question that in many (if not most) cases either preoperative stretching by the gland itself or operative trauma has rendered the internal sphincter permanently functionless. And if, as we have every reason for believing, preoperative weakening or atrophy of the external sphincter fibers has taken place, it is obvious that no degree of surgical finesse can prevent that which has already taken place.

It is difficult to imagine how any variation in suprapubic technique could in any way tend to prevent (or cause) postoperative incontinence. Yet control difficulties are observed following the suprapubic procedure. We have under observation at the present time a patient (our own) with post-suprapubic prostatectomy incontinence, now with good control, but not until after many months of treatment. Goldstein and Rubin[7] have recently reported 3 similar cases. The same applies to the transurethral route. There is nothing by way of prevention that the transurethral operator is able to do excepting avoid carrying his incisions below the apex of the prostate, and this the skilled resectionist is able to do with reasonable certainty.

Insofar as the perineal approach is concerned, one can do no more than employ meticulous care in the dissection in avoiding retraction pressure upon the perineal nerve and in avoiding possible injury to nerve fibers during plastic closure by employing fine gut loosely tied. Such sutures serve no purpose whatever excepting approximation of tissues and obliteration of spaces. Therefore, failing in methods of prevention of what already has taken place, we are confronted with the question as to what may be done by way of treatment.

TREATMENT

As is well known, the type of incontinence under discussion (excluding neurogenic dysfunction and surgical trauma to muscle fibers or perineal nerves) tends toward spontaneous recovery over a period of several days to several weeks, although occasionally much longer delayed. Recovery may take place, however, under treatment not instituted until after many months of leakage (Verges-Flaque[8]).

The natural or spontaneous process of recovery may be materially hastened by a program consisting essentially of explanation, instruction and encouragement, designed with a view to strengthening the external sphincter fibers by voluntary exercise. Progress in this program for obvious reasons depends largely upon the mental capacity and the general physical condition of the individual patient. Of first importance is explanation to the patient as to why the sphincter fibers are weak, and why voluntary effort is necessary. The sphincter muscle weakness is compared to general physical weakness known to result from a very brief confinement to bed, and known to disappear rapidly with exercise. It is explained that the effort necessary to contract the sphincter is the same as that to control loose bowels, and that this effort may be momentarily made many times daily, with or without relationship to urination. The patient is urged to allow urine to accumulate in the bladder while he is in the sitting or recumbent position, and then upon rising to make repeated attempts alternately to start and stop the urinary stream. The Cunningham clamp is sometimes helpful in enabling the patient to acquire a full bladder. Progress is not infrequently noted with the first "lesson," with resulting encouragement and increased effort. The patient did not know he could accomplish this. He had not tried. Strychnine* in full dosage, we believe to be helpful in restoring muscle tone.

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[7] Goldstein, A. E. and Rubin, S. W.: Incontinence following suprapubic prostatectomy, with report of three cases. Urol. and Cut. Rev., 50: 664, 1946.

[8] Verges-Flaque, A.: Urinary incontinence following prostatectomy: its cure by non-operative treatment, J. Urol., 61: 96, 1949.

In the more difficult cases the bladder is daily filled to capacity through a catheter, and the same start-stop, start-stop practice repeated. Close personal supervision is essential. The more intelligent and receptive the patient, the more rapid the progress. By contrast, the greatest difficulty is encountered, and the utmost in patience and perseverance required, in cases of senile mental deterioration associated with general physical weakness and debility, where understanding and cooperation, and both the will and the strength to help are lacking.

Verges-Flaque[8] has very recently directed attention to this type of incontinence, "which may follow any type of prostatic surgery," and has outlined an essentially similar program of sphincter exercise treatments, reporting 10 cases, 5 cures, 4 good results, and 1 total failure. It is of particular interest to note that in only two of these cases was the duration of incontinence less than 11 months prior to the institution of treatment. This article also includes a description of pre-treatment, endoscopic and cystometrographic studies determining the ability of the external sphincter to contract, and the "maximum sphincteric contraction pressure," thus supplementing clinical observation with scientific data.

Another very recent and valuable contribution to this subject by Rolnick and Arnheim[9] is a "histo-anatomical study of the external urethral sphincter . . . with special reference to incontinence following prostatic surgery," which supports the theory that external sphincter damage is not the sole factor in post-prostatectomy incontinence. These authors agree that since "the apex of the prostate is enveloped by the external sphincter" which is *extra*capsular, and since all varieties of prostatectomy (suprapubic, perineal, retropubic and transurethral) are *intra*capsular, "direct injury to the external sphincter should not occur in any of these procedures." They consider pressure by a hemostatic bag or pack as a possible injurious factor, although this type of incontinence is noted where neither has been employed. These authors also suggest, having demonstrated by careful measurements of a large number of autopsy specimens that the average verumontanum-external sphincter distance is only 9 mm., and "the depth of sphincter in membranous urethra" only 2 mm., that "thermal penetration in electroresection" is a factor in incontinence, "even though the external sphincter has not been cut."

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* Strychnine sulf., 3 grains; fld. ext. ergot., 2 ounces; ephedrin Sulf., 8 grains; arom. elixir q.s. 8 ounces, given in teaspoonful dosage, 4 times daily.

[9] Rolnick, H. C. and Arnheim, F. K.: An anatomic study of the external urethral sphincter in relation to prostatic surgery. J. Urol., 61: 591, 1949.

SUMMARY

Temporary urinary incontinence (exclusive of neurogenic dysfunction) may follow the surgical removal of obstructing prostatic tissue by whatever route, regardless of surgical finesse.

Incontinence of this type occurs independently of surgical injury to external sphincter or its nerve supply, and may reasonably be ascribed to preoperative weakness or atrophy of the external sphincter, resulting from months or years of disuse, while relieved of duty by the obstructing prostate.

There is obviously no method of prevention of that which has already occurred, although plication of the transversus fibers during perineal enucleation may be helpful.

Sphincter "exercise" treatments, personally supervised, and systematically carried out tend materially to shorten the period of incapacity.

External sphincter weakness thus may be considered to have been caused and concealed by the obstructing prostate, and merely revealed by prostatic surgery.

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BACTERIAL ENDOCARDITIS AS A COMPLICATION OF TRANSURETHRAL PROSTATIC RESECTION

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In a review of nonurologic complications following transurethral prostatic resection in 1946, 3 cases of bacterial endocarditis were found. This finding was the stimulus for the present review, which is an effort to determine the frequency of occurrence of this complication. Considering the age and general debility of many of the patients for whom the operation is performed, the mortality rate compares favorably with that of other surgical procedures of comparable magnitude. However, further efforts should be made to reduce the number of complications.

Isolated cases of infection of the blood stream after urethral manipulation have been reported over the past 60 years. It was not until 1929 that Scott demonstrated the frequency with which bacteremia or septicemia followed urethral instrumentation. He reported 82 cases in which results of culture of specimens of blood were positive, and in 51 of the cases the infection had followed instrumentation of the urethra. Barrington and Wright reported that results of culture were positive 13 times after 23 urethral manipulations involving 18 patients. Hyman and Edelman have emphasized the seriousness of coccic septicemias as compared to bacillary infections of the blood stream. They reported 13 deaths (68.4 per cent) among 19 patients who had coccic infections after urethral manipulation and only 9 deaths (20 per cent) among 45 patients who had bacillary infections after such procedures. The incidence of bacteremia after urethral instrumentation is 10 per cent, according to Powers. More recently, Creevy and Feeney carried out blood culture at the end of transurethral prostatic resection, and also whenever a severe febrile reaction occurred, in a series of 350 patients. Bacteria could be cultured in 45.4 per cent of the specimens of blood. They stated that postoperative infection is the most frequent complication of transurethral resection. Meneely reported 2 cases in which bacterial endocarditis followed urethral manipulation. McLaughlin and co-workers listed the causes of death of 16 patients who died after transurethral prostatic resection. Six patients died with septicemia and 1 of these had acute mitral bacterial endocarditis caused by Staphylococcus aureus. Biorn carried out blood culture at the end of transurethral prostatic resection in 106 cases, in 13 (12.3 per cent) of which results of culture were positive. Results of culture were negative in all cases 48 hours postoperatively. It is apparent that transient bacteremia is a common occurrence after urethral manipulation or transurethral prostatic resection.

Acute or subacute bacterial endocarditis occurred 8 times after transurethral prostatic resection performed at the Mayo Clinic in the years 1944 to 1948, inclusive (table 1). These cases will be reported in some detail.

REPORT OF CASES

Case 1.—A 66 year old man was admitted to the Clinic on June 12, 1944 because of pain in the right knee and symptoms of urinary obstruction. He had suffered from rheumatic fever at the age of 19 years. A systolic murmur was heard over the precordium; the valve involved was not mentioned. Two infected teeth were extracted on June 15, 1944. On June 19, transurethral prostatic resection was performed, 12 gm. of tissue being removed. Culture of the urine was not done. Chills and fever were noted on the second postoperative day, and continued until the patient was discharged on July 15, 1944. Blood culture produced Streptococcus faecalis on June 22, 1944, and on ten other occasions before the patient was dismissed. While the patient was home subconjunctival hemorrhages were noted. He received 200,000 units of penicillin daily from June 24 to July 15, 1944. He also received sulfadiazine and mandelic acid by mouth. Sensitivity of the organism to penicillin was not determined. The patient died at home in July 1944. The diagnosis was subacute bacterial endocarditis on chronic rheumatic endocarditis.

TABLE 1. *Bacterial endocarditis after transurethral prostatic resection*

CASE	PREOPERATIVE MURMUR	VALVE INVOLVED	ACUTE OR SUBACUTE	ORGANISM	RESULT
1	+	?	Subacute	S. faecalis	Died
2	–	Aortic	Subacute	S. faecalis	Died
3	+	Mitral	Subacute	S. faecalis	Died
4	+	Aortic	Acute	M. pyogenes	Died
5	+	Mitral	Subacute	S. faecalis	Died
6	+	Aortic	Acute	S. faecalis	Died
7	+	Mitral	Subacute	S. faecalis	Recovered
8	+	Aortic	Subacute	S. faecalis	?

Case 2.—A 61 year old man was admitted to the Clinic on November 23, 1944, complaining of symptoms of urinary obstruction. A cardiac murmur was not heard and culture of the urine was not done preoperatively. On December 5, 1944, transurethral prostatic resection was carried out in which 69 gm. of tissue was removed. On December 10, after removal of an indwelling catheter, the patient experienced a chill and fever. The fever continued until December 14, but the temperature was normal thereafter until the patient was discharged from the hospital on December 22. On December 13 blood culture produced Micrococcus pyogenes (Staphylococcus aureus). The patient received penicillin by continuous intravenous drip infusion from December 14 to 20. Results of blood culture on December 15 and 20 were negative. The patient was dismissed from the Clinic on December 26, 1944. He returned on February 14, 1945, complaining of epigastric distress, nausea and weakness of 1 week's duration. At this time an aortic systolic and diastolic murmur was heard. Blood culture on February 15, 21 and 24 produced Streptococcus faecalis. The organism was sensitive to between 1 and 10 units of penicillin per cubic centimeter. The patient

was admitted to the hospital, where he continued to have a low-grade fever in spite of the fact that he received penicillin by continuous intravenous drip infusion in doses of 100,000 units daily from March 4 to 20. The diagnosis was "subacute bacterial endocarditis involving the aortic valve due to Streptococcus faecalis." He was dismissed, but it was not felt that his condition had been brought under control. Later he died at home.

Case 3.—A 48 year old man was admitted to the Clinic on February 5, 1946, complaining of frequency of urination, nocturia, dysuria and perineal pain. A soft systolic apical murmur was noted. Seven grams of tissue was removed by transurethral prostatic resection on March 4, 1946. Secondary resection was performed on March 15, 1946. The convalescence was satisfactory. The patient returned on August 7, 1946, complaining of a slow urinary stream. This was regarded as the result of contracture of the vesical neck. He also complained of some loss of weight, and occasional pain in the left shoulder and left side of the thorax not related to exertion. On August 10, 1946, the vesical neck contracture was resected; 2 gm. of tissue was removed. Postoperatively, the patient had a shaking chill and temperature as high as 104F. He was dismissed on August 14, but returned to the hospital on August 16 because of low grade fever and lumbar pain. The fever subsided after 4 days' treatment with penicillin in doses of 160,000 units per 24 hours. The patient was discharged on August 23 and returned again to the hospital on October 10, 1946. His complaints at this time were fever, weakness, loss of weight and a tender area over the terminal phalanx of the left middle finger. The heart was enlarged; a coarse systolic murmur was heard loudest at the apex and was transmitted toward the axilla. Petechiae were found in the mucous membranes of the mouth and in the ocular fundi. Culture of the urine gave negative results at this time; however, blood culture carried out seven different times produced Streptococcus faecalis. Penicillin was administered from October 17 to November 1 in doses of 480,000 units daily. On November 1 the dose was increased to 4,000,000 units daily by continuous intravenous drip infusion. At this time the temperature became normal and four blood cultures done at four different times gave negative results. On November 28 the use of penicillin was discontinued; on December 3 and 5 the culture of specimens of blood again produced Streptococcus faecalis. The administration of penicillin was started again on December 6, in doses of 4,000,000 units daily. On December 10 the patient was awakened by a severe headache, and he lapsed into coma. He did not move the left arm and leg. Death ensued 6 hours later. The organism cultured from the blood was sensitive to penicillin in concentrations between 0.8 and 1.5 units per cubic centimeter. Necropsy disclosed subacute bacterial endocarditis caused by Streptococcus faecalis involving the mitral valve, which was chronically thickened. There was also a rupture of a mycotic aneurysm of a branch of the right middle cerebral artery, with cerebral hemorrhage. There were infarcts of the spleen and right kidney.

Case 4.—A 78 year old man was admitted to the hospital on March 11, 1946, complaining of a poor urinary stream of 2 years' duration. In November

44, he had undergone transurethral prostatic resection elsewhere. Symptoms
urinary obstruction had persisted, requiring urethral dilatations. For 4 weeks
ior to his admission he had catheterized himself twice daily. Systolic and di-
tolic murmurs were heard loudest at the aortic area. On March 13, 1946, trans-
ethral prostatic resection was performed, with removal of 12 gm. of tissue,
hich was reported as adenocarcinoma. Fever was noted on the day of
e operation, and it continued until the death of the patient. Penicillin was ad-
inistered in doses of 120,000 to 400,000 units daily from March 14 to 18, in-
lusive. Culture of the urine was not done preoperatively. On March 15 and 17
esults of blood culture were positive for Micrococcus pyogenes (Staphylococcus
ureus), large numbers of organisms being produced. This organism was not sen-
itive to penicillin in concentrations of 100 units per cubic centimeter. The pa-
ient died on March 19, 1946. Necropsy revealed acute vegetative bacterial en-
locarditis of the aortic valve caused by Micrococcus pyogenes, calcification of
he aortic leaflets with extension to the mitral ring, widespread metastatic ab-
cesses, and coronary sclerosis with a healed posterior basal myocardial infarct.
The mitral valve showed changes of chronic rheumatic endocarditis.

Case 5.—A 73 year old man was seen on December 14, 1946, because
f symptoms of urinary obstruction of 3 years' duration. He was found to have
coarse systolic murmur at the apex; roentgenoscopic examination of the left
uricle disclosed it to be enlarged. Culture of the urine was not done preoper-
tively. It was suggested that penicillin be administered prophylactically at the
ime of surgical treatment; but this was not done. On December 16, 1946, trans-
rethral prostatic resection was performed and 43 gm. of tissue was removed.
onvalescence was satisfactory until December 23, when fever was noted which
persisted until the discharge of the patient from the hospital on January 14,
1947. Penicillin in beeswax was administered intramuscularly from December 23
to 27, in doses of 300,000 units daily. Sodium mandelate was administered in-
travenously in doses of 15 gm. daily on 4 occasions later in December, with no
effect on the bacteremia. Blood culture produced Streptococcus faecalis on December 27 and 30, 1946, and again on January 2 and 14, 1947. Culture of the urine on January 3, 1947, produced Streptococcus faecalis and Escherichia coli. Blood culture on January 11 gave negative results. Penicillin was again given intramuscularly in doses of 1,800,000 units daily from January 6 to 13. The diagnosis was "subacute bacterial endocarditis on chronic rheumatic mitral endocarditis." The patient died at home approximately 1 month after he had been dismissed from the hospital. Necropsy was not performed.

Case 6.—A 63 year old man was admitted to the Clinic on May 12, 1947, because of symptoms of urinary obstruction of 2 years' duration. A systolic murmur, loudest at the aortic area, was noted over the precordium, and the second aortic sound was absent. Preoperative culture of the urine gave negative results. On May 15, 1947, 30 gm. of adenomatous prostatic tissue was removed by transurethral resection. A low grade fever was noted on the day of operation, and it persisted until his death. Blood culture on May 26 and 27 produced Streptococcus faecalis. This organism was sensitive to penicillin in concentrations between 1.6 and 3.2 units per cubic centimeter. It was sensitive to streptomycin in concentrations between 12 and 25 units per cubic centimeter. Penicillin was administered in doses of 320,000 units per 24 hours from May 20 to 24. Penicillin in doses of 4,000,000 units daily and streptomycin in doses of 2 gm. daily were administered from May 27 to June 5. Digitalis was also administered because of signs of cardiac failure. No petechiae were noted. On May 27, culture of the urine produced Aerobacter aerogenes. Death occurred rather suddenly on June 5, and was accompanied by convulsive dyspnea. It was thought to be due to massive pulmonary embolism associated with acute bacterial endocarditis involving the aortic valve, the site of calcareous aortic stenosis.

Case 7.—A 68 year old man presented himself on November 4, 1947, complaining of difficult urination. In October 1946, he had undergone transurethral prostatic resection elsewhere. After this, contracture of the vesical neck had developed, requiring the passage of sounds at monthly intervals. A harsh systolic murmur was heard loudest at the apex. On November 17, the urethra was dilated and 7 gm. of tissue was removed by transurethral prostatic resection. Penicillin was administered in doses of 160,000 units daily from November 11 to 22. The patient was dismissed on December 1, after a normal convalescence.

He returned on March 9, 1948, stating that soon after returning home he had noted a low grade afternoon fever. Pain in both hips, increased dyspnea on exertion, orthopnea and slight edema of the ankles also had developed. Three days prior to his second admission he had noted numerous petechial lesions over the lower extremities. On examination the heart was found to be slightly enlarged, and a coarse systolic murmur was heard loudest over the apex, but also over the aortic area. The murmur was not transmitted to the vessels in the neck, and the second aortic sound was normal. Fading petechiae were seen over the lower extremities. Elevation of the temperature to 100.4F in the afternoon was noted. On March 10 and 19 culture of the urine produced Escherichia coli; on March 19 and 22 blood culture produced Streptococcus faecalis. This organism was sensitive to penicillin in concentrations between 1.5 and 3.0 units per cubic centimeter. Penicillin was administered by continuous intravenous drip infusion from March 20 to 23 in doses of 1,000,000 units daily. This dose was increased to 10,000,000 units daily on March 24 and the dose was continued through April 8. On April 4 the patient had noted pain found to be caused by embolism in the palm of the left hand. After the institution of penicillin therapy the fever gradually subsided. Results of blood culture done on 8 occasions were negative from March 24 to April 26. The patient was again seen in February 1949, at which time he did not have symptoms such as those recorded previously. The diagnosis was "subacute bacterial endocarditis of the mitral valve superimposed on chronic rheumatic mitral endocarditis."

Case 8.—A 68 year old man was seen in November 1948, complaining of symptoms of urinary obstruction of 2 years' duration. A harsh systolic murmur was heard loudest at the aortic area, and was transmitted to the vessels of the neck. The intensity of the aortic second sound was decreased, and a thrill was felt at the aortic area. Preoperative culture of the urine was not done. A large vesical calculus was removed by suprapubic cystostomy on December 4, 1948 (fig. 1). On December 14 transurethral prostatic resection was performed, with the removal of 39 gm. of tissue. Procaine penicillin was administered in doses of 300,000 units intramuscularly once daily from December 15 to 19. The patient was dismissed from the hospital on December 24, after an uneventful convalescence.

Because of mild dysuria the patient returned on December 29 for lavage of the bladder; this was done again on January 7, 8 and 10, 1949. The patient first noted afternoon fever on January 8 and this fever continued until he re-entered the hospital on January 18. Other symptoms noted were pain in the neck, chest, shoulders and fingertips. Splinter hemorrhages also were noted at the time of this re-admission, and blood and urine cultures produced Streptococcus faecalis on January 18. This organism was not inhibited by streptomycin in a concentration of 25 micrograms per cubic centimeter. It was sensitive to penicillin in concentrations of 1.6 units per cubic centimeter and aureomycin in concentrations of 1.5 micrograms per cubic centimeter. Aureomycin was administered by mouth in doses of 4 gm. per 24 hours from January 20 to 25. On the latter date the dose was reduced to 3 gm. per 24 hours and was continued from January 26 to February 10. Results of blood culture were negative on January 24 and 27 and February 1, 7 and 14. On February 24, 25 and 28 blood culture again produced Streptococcus faecalis, and splinter hemorrhages again were noted. Aureomycin once more was given orally in doses of 3 gm. daily, from February 26 to March 25. Results of blood culture were negative on March 5 and 18. On

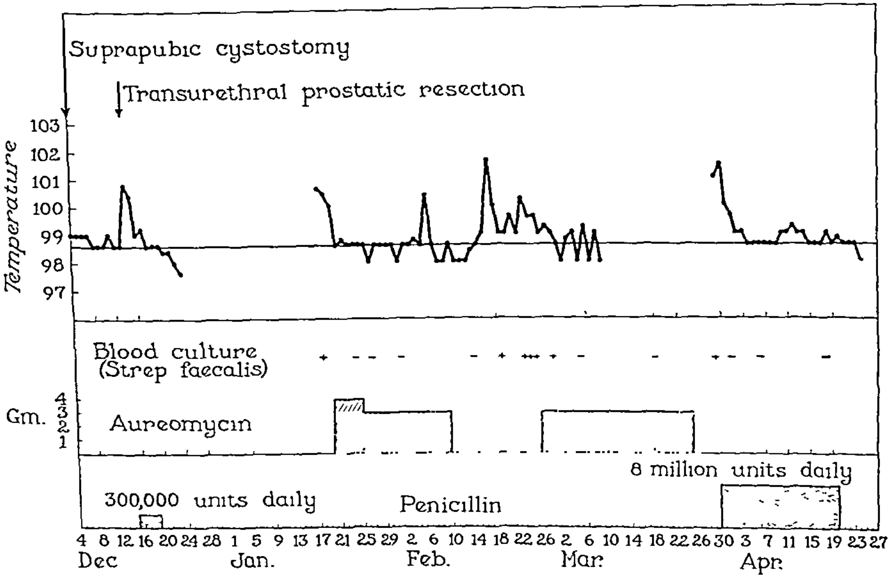

FIG. 1. Clinical and laboratory data: subacute bacterial endocarditis after transurethral prostatic resection in case 8.

March 26 and 29 blood culture again produced Streptococcus faecalis. Urine culture had given consistently negative results after January 27. Penicillin was then administered by continuous intravenous drip infusion in doses of 8,000,000 units per 24 hours from March 30 to April 20. The total dose of penicillin was 168,000,000 units. Fever invariably disappeared and the patient's general condition improved when he received either aureomycin or large doses of penicillin. The content of penicillin in the blood was 32 units per cubic centimeter on April 1. The diagnosis was "calcareous aortic stenosis and subacute bacterial endocarditis involving the aortic valve."

COMMENT

There were 8 cases of bacterial endocarditis (table 1), in 2 of which the disease was acute and in 6 of which it was subacute. An organic type of heart murmur was heard preoperatively in 7 of the 8 cases. The mitral valve was involved in 3 cases, the aortic valve in 4 cases, and the valve involved was not determined in 1 case. Streptococcus faecalis was the causative organism in 7 cases and Micrococcus pyogenes (Staphylococcus aureus) was demonstrated in 1 case. Six of the 8 patients died either in the hospital or soon after returning home. One patient was well 10 months after dismissal, and at the time of this report it was too early to evaluate the result of treatment in 1 case. Only 1 patient of this group received antibiotic agents prophylactically, and that patient received such an agent in inadequate doses, considering the resistance of the organism found. Necropsy was carried out in 2 of the 3 patients who died in the hospital; this examination was not carried out in the 3 who died at home.

The incidence of bacterial endocarditis after transurethral prostatic resection is relatively low. The disease has occurred only 8 times, to our knowledge, after approximately 7,000 operations during the 5-year period from 1944 through 1948. The possibility of the occurrence of this complication is always present in any case in which urethral instrumentation is done and in which valvular heart disease is present.

The incidence of bacteriuria is high among patients who have obstruction of the vesical neck. The organisms most commonly found in the urinary tract are Escherichia coli, Aerobacter aerogenes, Proteus ammoniae, Pseudomonas aeruginosa, Micrococcus pyogenes (Staphylococcus aureus) and Streptococcus faecalis. If bacteremia occurs in 45 per cent of the patients postoperatively as reported by Creevy and Feeney, there would seem to be a fertile field for the development of bacterial endocarditis, especially in those patients having scarred heart valves. In our experience, the organisms most commonly causing fatal complications are Streptococcus faecalis and Micrococcus pyogenes. Both these organisms usually are highly resistant to treatment with ordinary doses of penicillin or streptomycin. Aureomycin, however, is an antibiotic which is very effective against both these cocci. It seems logical to use aureomycin prophylactically before and after transurethral prostatic resection for patients who have evidence of chronic endocarditis. This is true whether the valvular lesion has a rheumatic or a degenerative basis, as may be the case in calcareous aortic stenosis. The exact dose of aureomycin when it is used prophylactically in such instances has not been determined. We have been using a dose schedule of 1 gm. of the antibiotic every 8 hours, beginning 9 hours prior to operation and continuing until the catheter has been removed permanently. Glaser and his co-workers have demonstrated that the administration of large doses of penicillin for 24 hours prior to dental extraction caused a significant decrease in the incidence of bacteremia after this operation, but failed to prevent it in a large number of cases. A similar situation may well exist in respect to the use of aureomycin prophylactically before transurethral prostatic resection. Nevertheless, it would seem to be worth while to carry out this program for patients with valvular heart disease who undergo prostatic resection.

During the same 5-year period a total of 70 patients who underwent transurethral prostatic resection were found to have valvular heart disease. Of the 8 patients with bacterial endocarditis concerned in this paper 7 were known preoperatively to have valvular lesions. Thus the apparent frequency of occurrence of bacterial endocarditis in patients with valvular lesions was 7 of 70, or 10 per cent.

SUMMARY

Bacterial endocarditis occurred 8 times after transurethral prostatic resection during the 5-year period from 1944 through 1948. During the same period about 7,000 such operations were carried out, giving an incidence for bacterial endocarditis of about 1 case per 1,000 operations.

Bacterial endocarditis was noted 7 times after transurethral prostatic resection performed for 70 patients with known valvular heart disease, and only once in a patient who had no demonstrable valvular lesion.

Streptococcus faecalis or Micrococcus pyogenes (Staphylococcus aureus) was the pathogenic organism in all cases of bacterial endocarditis.

It would seem logical to administer aureomycin prophylactically before and after transurethral prostatic resection to all patients who have valvular heart disease.

REFERENCES

BARRINGTON, F. J. F. AND WRIGHT, H. D.: Bacteriemia following operations on the urethra. J. Path. & Bact., 33: 871–888, 1930.

BIORN, C. L.: Personal communication.

CREEVY, C. D. AND FEENEY, M. J.: Infection following transurethral resection of prostate gland. Bull. Univ. Minnesota Hosp. & Minnesota Med. Foundation, 20: 314–327, 1949.

GLASER, R. J., DANKNER, A. AND MATHES, S. B.: Effect of penicillin on bacteriemia following dental extraction. Am. J. Med., 4: 55–65, 1948.

HYMAN, A. AND EDELMAN, L.: Medical and surgical aspects of hematogenous infections in urology. J. Urol., 28: 173–198, 1932.

MCLAUGHLIN, W. L., BOWLER, J. P. AND HOLYOKE, J. B.: The causes of death following transurethral resection of the prostate. J. Urol., 59: 1233–1238, 1948.

MENEELY, J. K., JR.: Bacterial endocarditis following urethral manipulation. New Eng. J. Med., 239: 708–709, 1948.

MERRITT, W. A. AND THOMPSON, G. J.: Medical complications following vesical neck resections. (Unpublished data.)

POWERS, J. H.: Bacteriemia following instrumentation of the infected urinary tract New York State J. Med., 36: 323–331, 1936.

SCOTT, W. W.: Blood stream infections in urology: A report of 82 cases. J. Urol., 21: 527–566 1929.

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URETHRAL DIVERTICULA IN PARAPLEGICS

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Diverticula of the urethra are of fairly common occurrence in the female, but survey of the literature has revealed a limited number of cases in males. A total of 197 male cases has been found (table 1), although there are probably others recorded, as well as many not reported. Classification of these cases discloses that 102 of the diverticula were situated in the anterior urethra, 57 of these being of congenital origin while 45 were acquired. Diverticula of the posterior urethra accounted for 95 of the total number with only 6 being congenital in origin, the remaining 89 having been acquired.

Twenty eight additional cases, all acquired diverticula of the anterior urethra, have been found in male paraplegics at this hospital, and discussion will be directed chiefly toward this series of cases.

ETIOLOGY

Most investigators have held that acquired diverticula of the anterior urethra develop on the basis of one or a combination of two factors: 1) obstruction, and 2) destruction of the urethral wall (by inflammation or trauma). The cases presented within this report can probably be explained on the latter basis since 26 of the 28 give a definite history of peri- (para) (sub) urethral abscess. In addition, all have probably been subjected to trauma of some degree incident to urethral instrumentation.

All of the 26 patients with urethral diverticula who had peri-urethral abscesses were on urethral catheter drainage at the time the abscess developed. Four occurred within a few days following the institution of urethral catheter drainage; one developed after 2 weeks' time; the remainder occurred between 2 and 17 months later; the average being 4½ months. Eleven of these abscesses drained into the urethra, 2 were subjected to incision and drainage, and 13 ruptured to the outside. Of the latter 13 cases, 9 developed persistent urethral fistulas and 6 of these underwent surgical excision. Only 3 of the 26 patients had recurrent peri-urethral abscesses.

In addition to the 26 abscesses which developed into diverticula, 28 other paraplegic patients without evidence of diverticular formation have given a history of peri-urethral abscesses, making a total of 54. There have been 402 patients admitted to this paraplegic service, thus giving an incidence of 13.4 per cent for peri-urethral abscesses. However, in fairness to the present system of caring for paraplegics in centers, it can be stated that only 23 of the 54 patients developed

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their abscesses while patients on this service, an incidence of 5.7 per cent which does not compare unfavorably with those statistics of 5.0 per cent and 8.5 per cent reported from other paraplegic services. In another paraplegic center Bors found an incidence of 5.7 per cent for peri-urethral abscesses associated with secondary urethral fistula and 0.7 per cent for peri-urethral abscesses without

TABLE 1. *Reported cases of urethral diverticula**

AUTHOR	DATE	ANTERIOR URETHRA		POSTERIOR URETHRA		Total
		Congenital	Acquired	Congenital	Acquired	
Sisk, I R	1924		1			1
Neugebauer, F	1924	1				1
Huddy, G T	1925		1			1
Castro	1926	1				1
Rabinovic, M	1927	2				2
Muller, A	1927		1			1
Nicholson, B B	1927		2			2
Tedenot and Sinneseal	1927		1			1
Lowsley and Gutierrez	1928	29	14		72	115
Epstein, G E	1928				1	1
Salleros and Vilar	1928				2	2
Mouatt, T B	1298	1		1		2
von der Becke	1928		1			1
McKay and Colston	1929	1	5		3	9
Alcock, N G	1929			1		1
Taveres et al	1929			1		1
Asteriades, T	1930		1			1
Ternovsky, S	1930	1				1
Langer, E	1930		1			1
Frontz, W	1931	1				1
Ritter and Leidel.	1931		1			1
Sosin, J	1931			1		1
Chwalla, R	1931	2				2
Waugh, J R	1932		1			1
Carlton, C H	1932		1			1
Irwin, W R	1932		1			1
Kavayama, Y	1932	1				1
Bloch, G	1932			1		1
LeComte and Herschman	1933	1			3	4
Campbell, M F	1933		2			2
Rocz, A	1933	3	1			4
Clark, J B	1936				1	1
Kretschmer, H L	1936	1				1
Casini, A	1936		1		1	2
Shafman, S A	1937	1				1
Revoir, J	1937				1	1
Tagariello, P	1937		1			1
de la Pena A	1938			1		1
Gauthier and Gavet	1938		1			1
Dozsa, E	1938	1			1	2
Mitrofanov, P P	1938	1				1
Iverson and Jorgensen	1938	1				1

TABLE 1—*Continued*

AUTHOR	DATE	ANTERIOR URETHRA		POSTERIOR URETHRA		Total
		Congenital	Acquired	Congenital	Acquired	
Geiringer and Zucker	1939	1				1
Nichita, et al.	1939	1				1
Kini, M. G.	1939				1	1
Kolbenheyer, Z.	1940				2	2
Temporal, A.	1940	2				2
Seymour, G. C.	1941		1			1
Delgado, R.	1942	1				1
McGavran	1942		2			2
Fagerstrom, D. P	1943		2			2
Rioseco and Vargas	1944	1				1
Trafton, H. M.	1945				1	1
Chiodin and Litmanovich	1946	1				1
Zide and Siegel	1946		1			1
Knox, W. G.	1947	1				1
Repman and Warren	1948		1			1
Pate and Bunts	1949		28			28
		57	73	6	89	225

* Lowsley and Guiterrez in a most comprehensive survey in 1928 collected 109 cases to which they added 6 of their own. In that series, original authorship of the collected cases was listed. Assistance of Dr. Lowsley and Dr. Alfonso Davalos in classifying those cases is gratefully acknowledged.

Many cases are encountered more than once in the literature, having been used by various authors to illustrate the particular phase of the problem in which they were interested. In such instances, insofar as possible, original authorship has been noted. In a few cases classification as to etiology is probably debatable.

fistulas. Of the 26 cases with diverticula that have a history of peri-urethral abscesses, only 3 developed their abscesses while on this service. So many urethral complications might speak against urethral catheter drainage. However, we believe that through the use of thoroughly trained technicians, adequate irrigation (including tidal drainage), and the use of small Foley catheters which are changed frequently, the complications will not be prohibitive. We, as well as most other urologists, also believe that in spite of the relatively high incidence of peri-urethral infection, much more is gained by the early establishment of proper bladder function by urethral drainage than is lost by a local complicating condition that can be corrected without too much difficulty in most cases.

Why 26 of the 54 abscesses should develop into diverticula while the remaining 28 resolved or obliterated without causing a urethral defect is not entirely clear. Fagerstrom's theory of neurogenic dysfunction might play a part. However, neurological study has revealed no general pattern to substantiate this. The spinal cord pathology in all cases was traumatic in origin and the levels of injury were located between C4 and L2, the majority being in the midthoracic region. The levels of injury were essentially the same in the group of peri-urethral abscesses which did not develop diverticula. It would seem that whether or not a diverticulum formed would depend almost solely upon the degree and extent of suppuration, destruction of tissue, and scar tissue replacement. The chief neurogenic element is probably that factor which results in tissue devitalization and poor healing response, as observed so frequently in the decubital ulcers of these unfortunate patients.

Other factors in the etiology were considered. The ages varied from 21 to 55 with an average age of 29. Twenty six of the patients were of the white race while 2 were Negroes, this racial distribution paralleling the admissions to the paraplegic wards. In no case was a urethral stricture found. Calculi were not considered a causative factor except in possibly 1 case. Other etiologic possibilities are devices for urinary control such as incontinence clamps and various types of urine receptacles that might result in obstruction to urinary outflow. One of the latter, referred to by patients as a "Texas Special" consists of a latex condom taped over the penis with the distal end of the condom being perforated and taped over rubber tubing. Aside from the evil of vascular changes in the penile tissues from strapping too tightly with adhesive tape, some degree of obstruction could result from the taping and/or the twisting of the redundant latex condom. Also considered was the prolonged maintenance of the rim of a metal urinal against the floor of the urethra in the penoscrotal area. On the basis of carefully taken case histories, none of these agents were found to be at fault in the primary formation of the diverticula except in probably 1 patient (case 8). It is conceivable that by continuous application they could very easily act as an obstructive factor which would promote enlargement of the urethral diverticula once it were formed. However, even this theory could not be substantiated. In the single case exception cited this patient noted the development of a progressively enlarging penoscrotal mass after wearing an incontinence clamp for several months. Examination endoscopically, roentgenographically and at operation revealed a fusiform urethral dilatation extending from the anterior scrotal margin almost to the external sphincter. However, the dilatation was incompletely divided into three near equal segments by a pseudosphincter between the middle and proximal one thirds and by a partial diaphragm between the middle and distal one thirds. These anatomical findings would not be expected if the dilatation was purely the result of obstruction (as from an incontinence clamp).

PATHOLOGY

The excised diverticula have all been examined histologically and the pathologic findings are rather uniform throughout all sections (fig. 1).

The normal pseudostratified columnar epithelium of this portion of the anterior urethra undergoes squamous metaplasia to become frankly epidermoid with varying degrees of keratinization. The spongy tissue shows marked replacement by fibrosis with obliteration of normal blood spaces but with proliferation of small thin wall blood vessels. The normal urethral glands cannot be identified. Occasional small foci of round cell infiltration are noted. The albuginea layer is thickened by fibrosis. Sections stained according to Van Gieson's technique demonstrate a loss of smooth muscle fibers.

The relationship of co-existing pathologic conditions of the genito-urinary tract is difficult to evaluate in paraplegics. However, one lead that seems significant is the presence of vesico-ureteral reflux. The mechanism of production of this pathological condition in paraplegics is not well defined. Neurogenic dysfunction interfering with normal ureteral peristalsis has been advanced as an etiologic basis for vesico-ureteral reflux, but it is not easy to correlate such a theory with the high percentage of cases showing unilateral reflux (63 per cent in our series of 39 cases). We favor a theory of prolonged infection involving the intramural portion of the ureter and resulting in a fibrotic rigidity that destroys the normal ureterovesical valvular action.

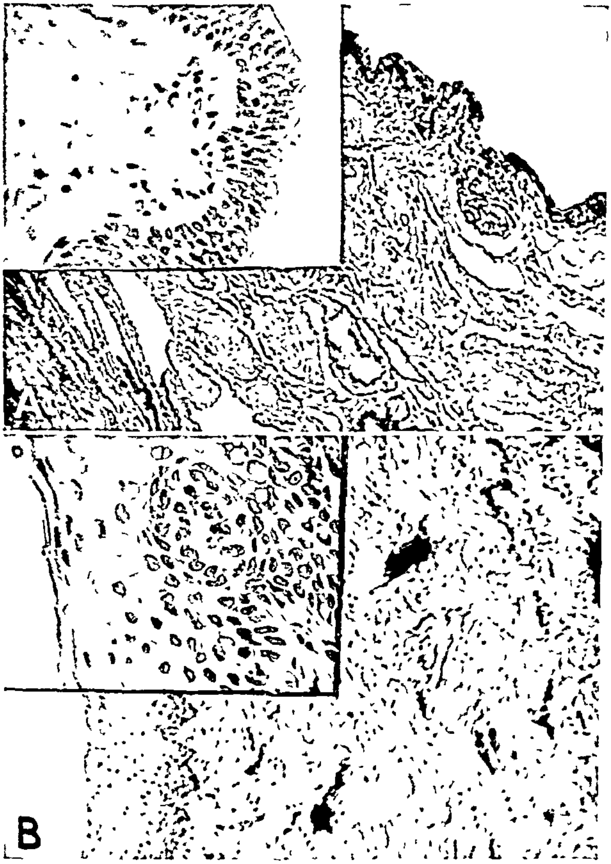

Fig. 1. *A*, tissue from normal urethra. *B*, tissue from urethral diverticulum

Of 114 paraplegics examined by cystogram, 39 patients (33 per cent) have shown x-ray evidence of vesico-ureteral reflux. Of the 28 cases of urethral diverticula herein reported, 10 patients (26 per cent) were found to have reflux. Four of these patients (cases 3, 5, 8 and 12) with long standing unilateral vesico-ureteral reflux have shown a loss of such reflux (2 to 12 months) following surgical correction of their urethral diverticula. Relief of obstruction to voiding by the operation is discounted because 3 of these 4 patients were on constant urethral catheter drainage before and after cystograms taken during the preoperative period had showed reflux, as well as in the postoperative period when they showed loss of reflux. Elimination of infection by the preliminary drainage and by excision of the diverticulum seems a more plausible explanation, but this too may be questionable.

One patient (case 15) with bilateral ureteral reflux died of pulmonary tuberculosis before a postoperative film was made. Two other cases with bilateral ureteral reflux are dead. One of these (case 16) had a large diverticulum while the other (case 27) had a well developed lesion, neither having undergone urethral diverticulectomy. Four other cases with urethral diverticula and unilateral vesico-ureteral reflux (cases 21, 22, 23 and 24) have refused surgical interference.

Of course, no conclusions can be drawn from this small number of cases. However, the loss of vesico-ureteral reflux in the 4 postoperative cases was thought significant enough to be mentioned.

SYMPTOMATOLOGY AND DIAGNOSIS

The most common objective and subjective symptom of urethral diverticula is the presence of a mass, which usually fills at the onset of micturition, and at the conclusion of the act may empty or the contents may be manually expressed. Other urinary symptoms consist of frequency, dysuria, pyuria, incontinence, prolongation of urination, tenesmus or vague pains. Pressure of the diverticulum against the urethra may cause difficulty in voiding and partial or complete retention. A persistent urethral discharge is not infrequent and rarely urethrorrhagia is a warning sign. Systemic symptoms with chills and fever may result from a badly infected diverticulum. Attention may be directed toward calculi within the sac. Bizarre sexual symptoms at times predominate and sterility caused by improper ejaculation has been the indication for investigation. Of course, there may be a complete lack of symptoms if the sac is of small size and empties well.

It can be readily understood that in paraplegics who are heirs to unstable urinary control, drainage tubes, urosepsis, etc., that such symptomatology is minimized, overshadowed and difficult to evaluate. Our attention was first focused upon this condition in paraplegics after 2 patients had noted a mass at the penoscrotal junction, again when 2 diverticula had been found on routine cysto-urethroscopy and after another was discovered during excision of a urethral fistula. After establishing the history of penoscrotal abscess in these cases, all patients with a history of peri-urethral abscess or severe urethral infection were surveyed for the presence of diverticula. During routine cysto-urethrography which was being conducted on this service in connection with a separate study directed toward establishing the incidence, etiology and treatment of vesico-ureteral reflux in paraplegics, additional diverticula were discovered. Others were found by routine cysto-urethroscopy. Eight of the 28 patients were aware of a mass. In 9 cases a mass was detected by examination of the patient while voiding and immediately afterwards. In the remaining 11 cases, due to an inability to void, etc., diagnosis was originally established by other means. Urethroscopic examination confirmed the presence of the diverticula in all cases. In the large majority of diverticula, a wide neck was observed, which is in keeping with the pathogenesis. Only in the larger diverticula was there evidence of poor drainage as manifested by the presence of purulent fluid and inflammation of the lining epithelium.

TREATMENT

The following methods have been used singly or in combination in the treatment of urethral diverticula:

a) Expectant: Occasionally small, asymptomatic diverticula are encountered and at times these are better left alone.

b) Nonoperative: The patient may be instructed in manual compression of the sac to prevent stagnation of urine. Irrigations and instillations of various antiseptic agents have been used, as well as urethral dilatations. These measures are purely palliative.

c) Operative: Enlargement of the neck of the diverticulum transurethrally or suprapubically has been reported as successful in a few cases, particularly in diverticula of the posterior urethra. However, although this procedure may promote better drainage, it does not eliminate entirely a basic anatomical alteration and careful follow-up is necessary to detect any progression in size, persistence of infection, or formation of calculi. Plication of the bulbocavernosus muscle to furnish support for a weakened urethral wall has been tried in 1 case as the sole form of treatment and failed. Invagination of the sac into the urethra has been advocated as a means of repair, but Kretschmer has aptly noted that due to the possibility of obstruction from the invaginated tissue, only very small diverticula could be treated in this manner. The treatment of choice is surgical excision of the sac with plastic repair of the urethra. In such an operative procedure diversion of the urinary stream is highly desirable if not almost mandatory.

Being aware of the latent or active infection in the urine of paraplegics and of their poor healing response, and having had some experience in attempting to close their almost intractable penoscrotal urethral fistulas, we approached this problem of urethral diverticula with some hesitancy and with considerable doubt as to what treatment, if any, would be best for the patients. In view of the fact that practically all of the diverticula opened into the urethra by a wide orifice, it was believed that perhaps there would be good drainage and no complications would ensue. However, it soon became apparent that in some cases the diverticula were steadily and even rapidly increasing in size. Also some were found to be grossly infected and obstructive in nature. In paraplegic patients due to the many known and unknown factors involved in upper urinary tract changes, it is somewhat difficult at times to say dogmatically what the pathogenesis is. However, recognizing at least the concomitant occurrence of upper urinary tract changes with the urethral diverticula, it was thought that surgical intervention was indicated certainly in those diverticula which were progressing in size and showing signs of gross infection. Many of the patients developed these indications even while on continuous urethral catheter drainage, as exemplified by case 16. While this patient unfortunately refused surgical treatment until too late, observation of the case showed the fatal results that may occur from this entity and its complications when allowed to progress without proper treatment.

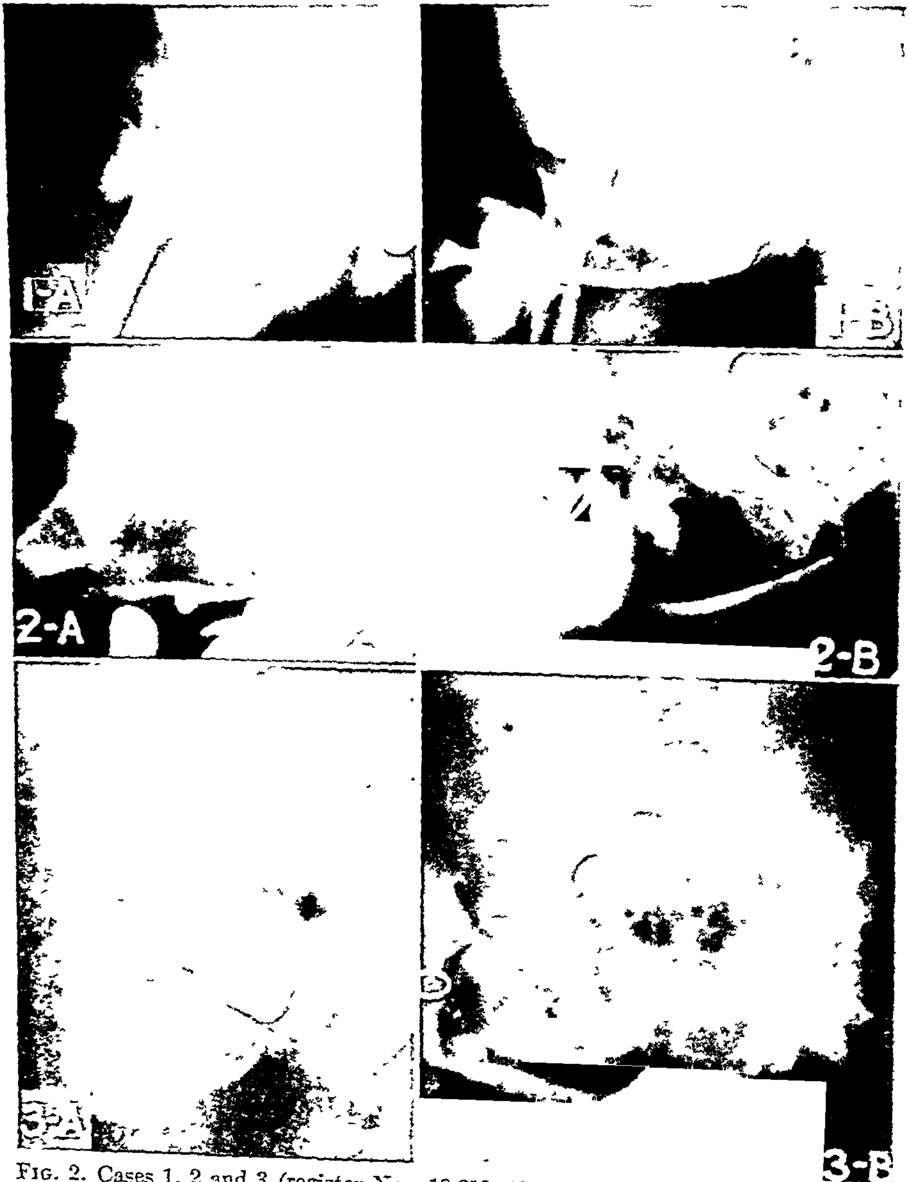

FIG. 2. Cases 1, 2 and 3 (register Nos. 18-216, 10-103, 160). *A*, preoperative; *B*, postoperative. Diverticulum in case 1 had capacity of 150 cc. Cases 1 and 2 are 1 year postoperative and are voiding with no residual. Case 3 still has urethral catheter due to inability to void, but vesico-ureteral reflux present for more than a year has now disappeared (not shown).

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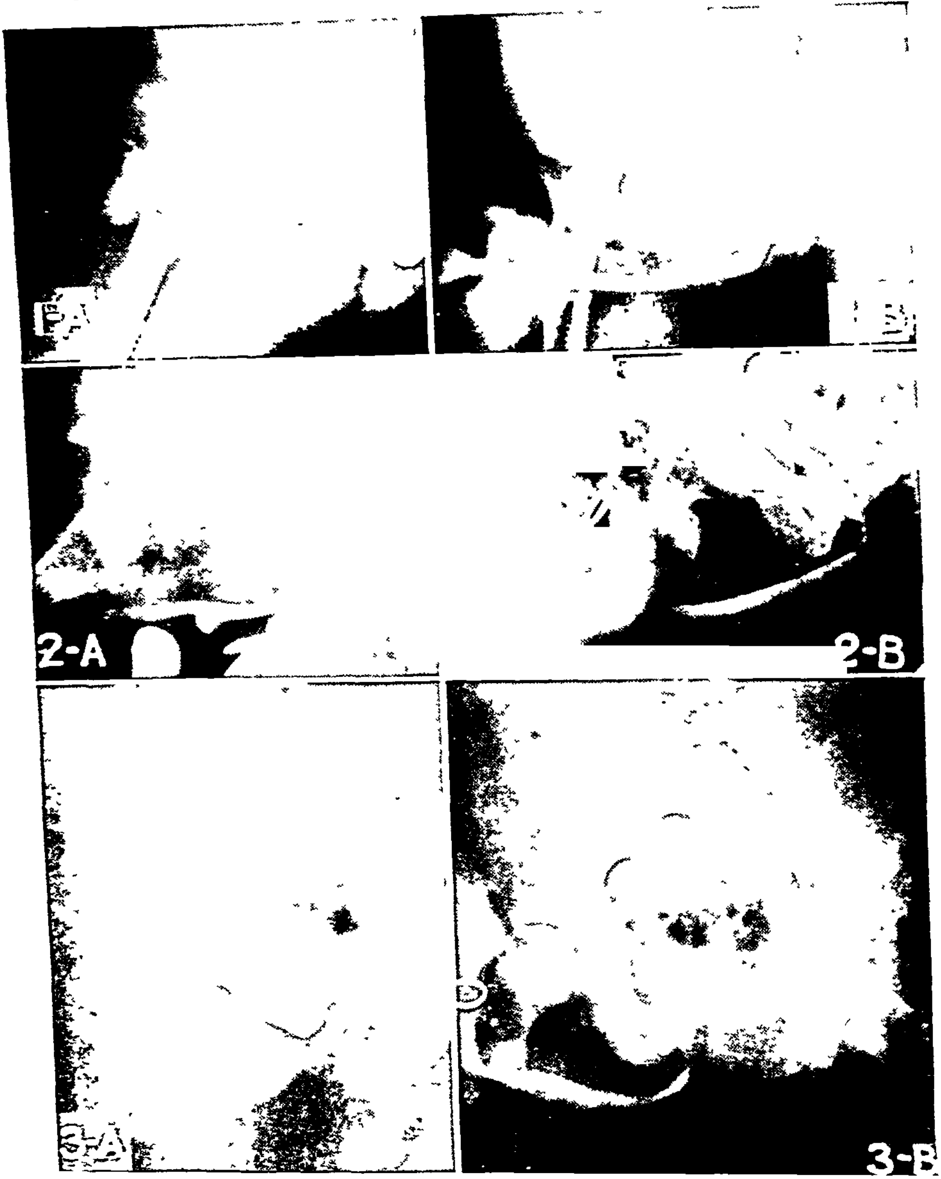

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until too late, observation of the case showed the fatal results that may occur from this entity and its complications when allowed to progress without proper treatment.

Since many of the patients had previously undergone prolonged suprapubic drainage and many already had varying degrees of physiologic and pathologic vesical changes, and as the diverticula were situated in the anterior urethra, diversion of urine was accomplished whenever possible by perineal urethrostomy. This drainage with local irrigations of the diverticulum, urethra, and bladder with antiseptic and antibiotic solutions was continued until the most favorable

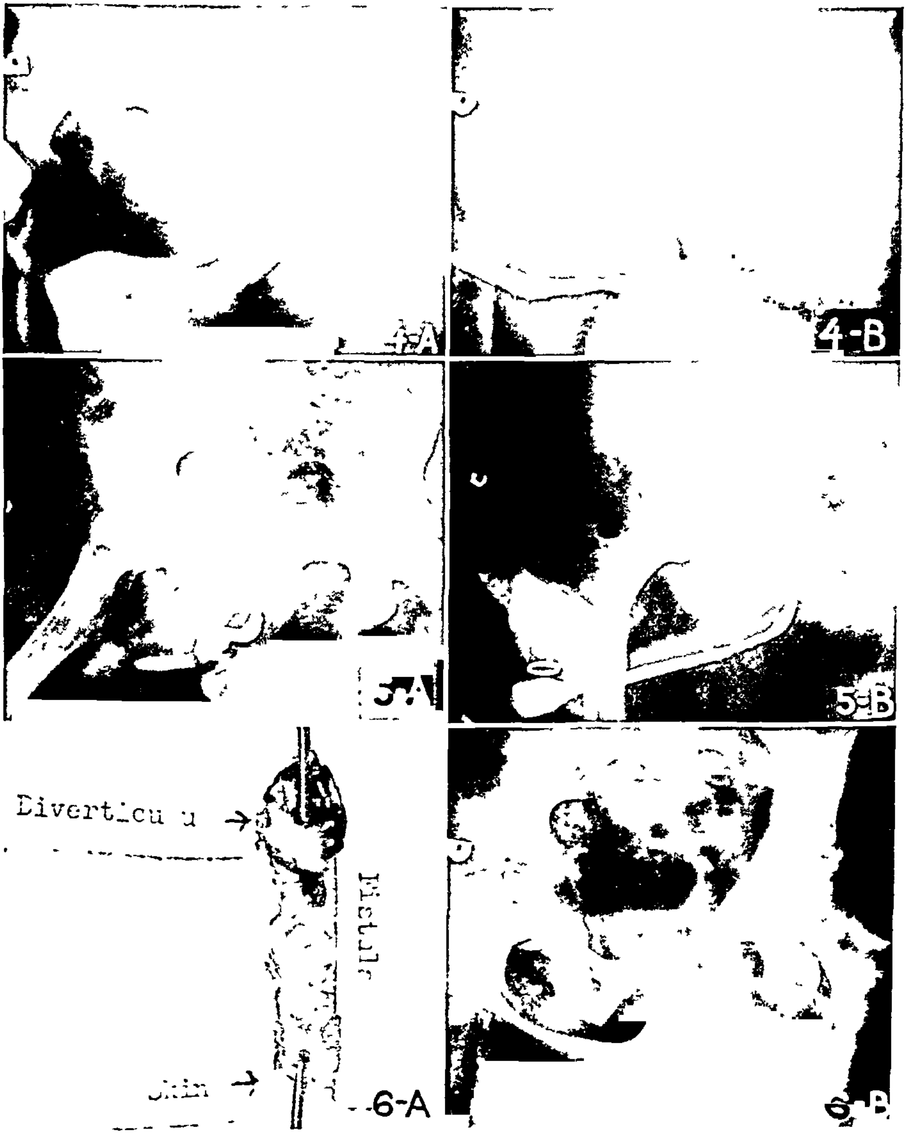

Fig 3. Cases 4, 5 and 6 (register Nos 144, 7474, 16-767) *A*, preoperative, *B*, postoperative. Indication in case 4 was persistent gross infection in sac along with renal insufficiency Unilateral vesico-ureteral reflux present in case 5 for 10 months has been absent since eradicating infected diverticulum Photograph of pathologic specimen substitutes for preoperative film in case 6

preoperative condition was attained. Anemia or hypoproteinemia when present was corrected. During the immediate preoperative phase, sulfonamides and anti-

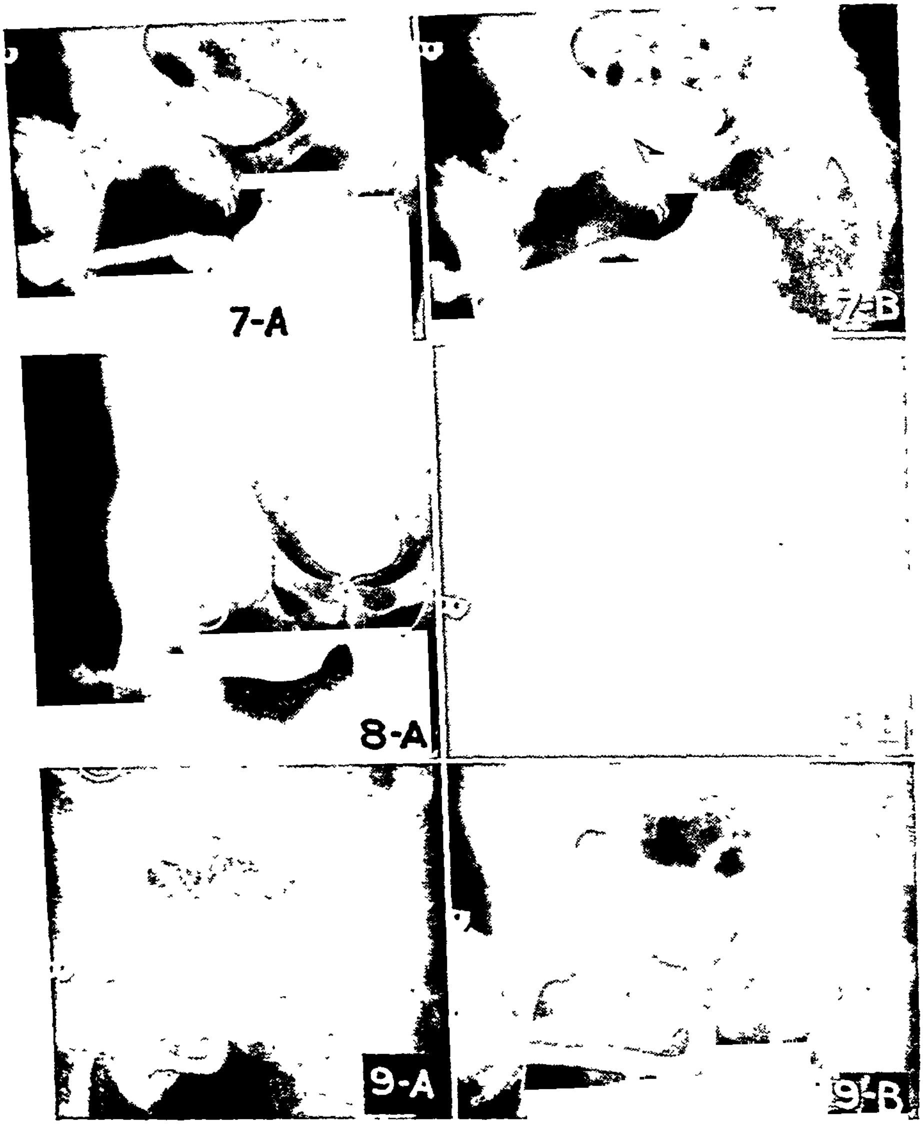

Fig. 4. Cases 7, 8 and 9 (register Nos. 130, 10-388, 112). *A*, preoperative; *B*, postoperative. All are now voiding with negligible residual. Case 8 gave no definite history of peri-urethral abscess but noted mass after using incontinence glamp for several months. Note absence of reflux postoperatively.

biotics were used to combat infection. Stilbestrol was administered to prevent penile erections.

Operative procedure is facilitated by the introduction of a 24F Foley catheter into the anterior urethra and inflating the bag within the diverticulum, thus distending the latter to near its capacity. A longitudinal incision is made over the bulge, including if present any scarring resulting from healed ostia of old urethral fistulas. The incision is extended through the subcutaneous fascia and Buck's fascia, these layers being dissected from the diverticular sac and at the same time

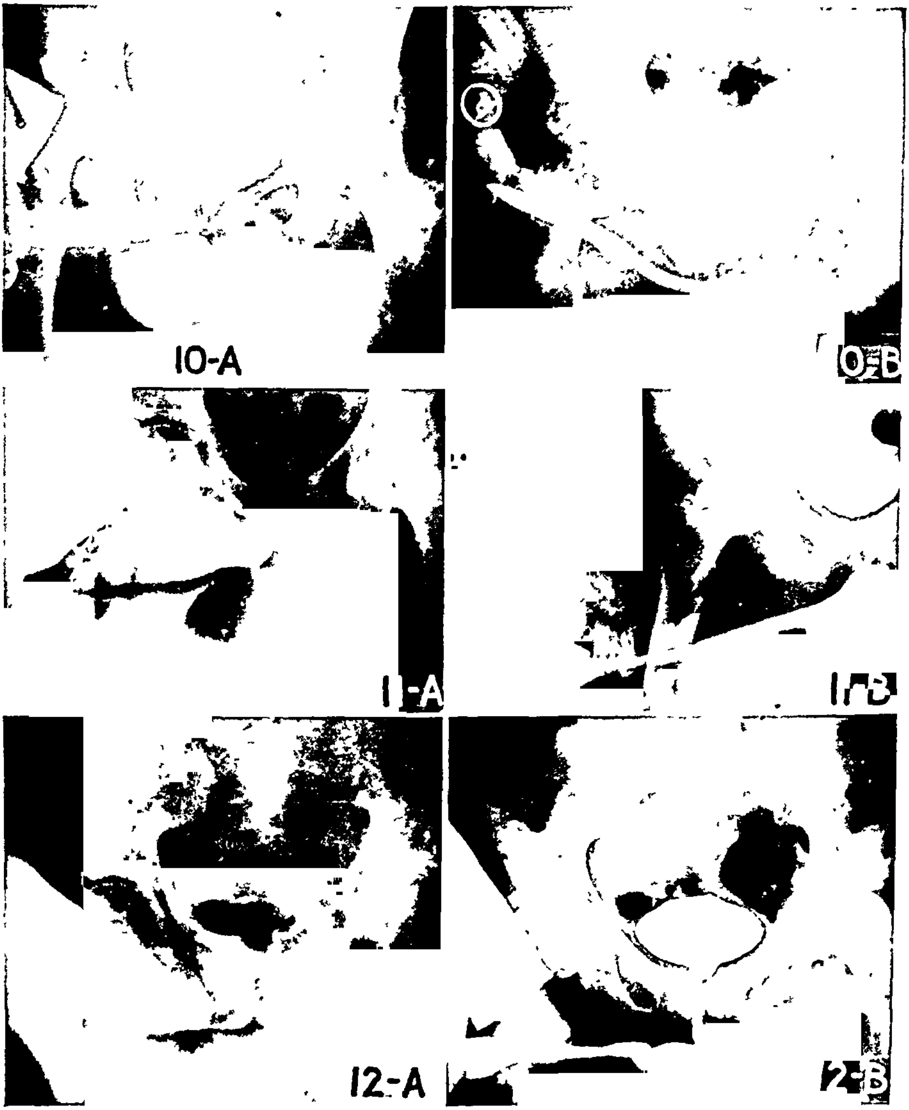

Fig. 5. Cases 10, 11 and 12 (register Nos. 128, 3931, 5071. *A*, preoperative; *B*, postoperative. All of these cases are now voiding with very little or no residual urine. Case 12 had not been able to void since injury despite two transurethral resections, and unilateral vesico-ureteral reflux noted for 1 year preoperatively has now disappeared.

dissecting free any fibrous tracts remaining from urethral fistulas. The diverticulum is freed on each side and proximally and distally to its connection with the urethra. The sac is incised longitudinally between points where the urethra is of normal caliber. After deflation of the Foley bag, the sac is trimmed on each side, leaving enough urethra to close over the 24F catheter without undue tension. Closure is then performed in layers with interrupted sutures, avoiding penetration of the urethral mucosa and being careful to invert this structure. Before suturing the superficial layers, any redundant tissue is excised to afford better

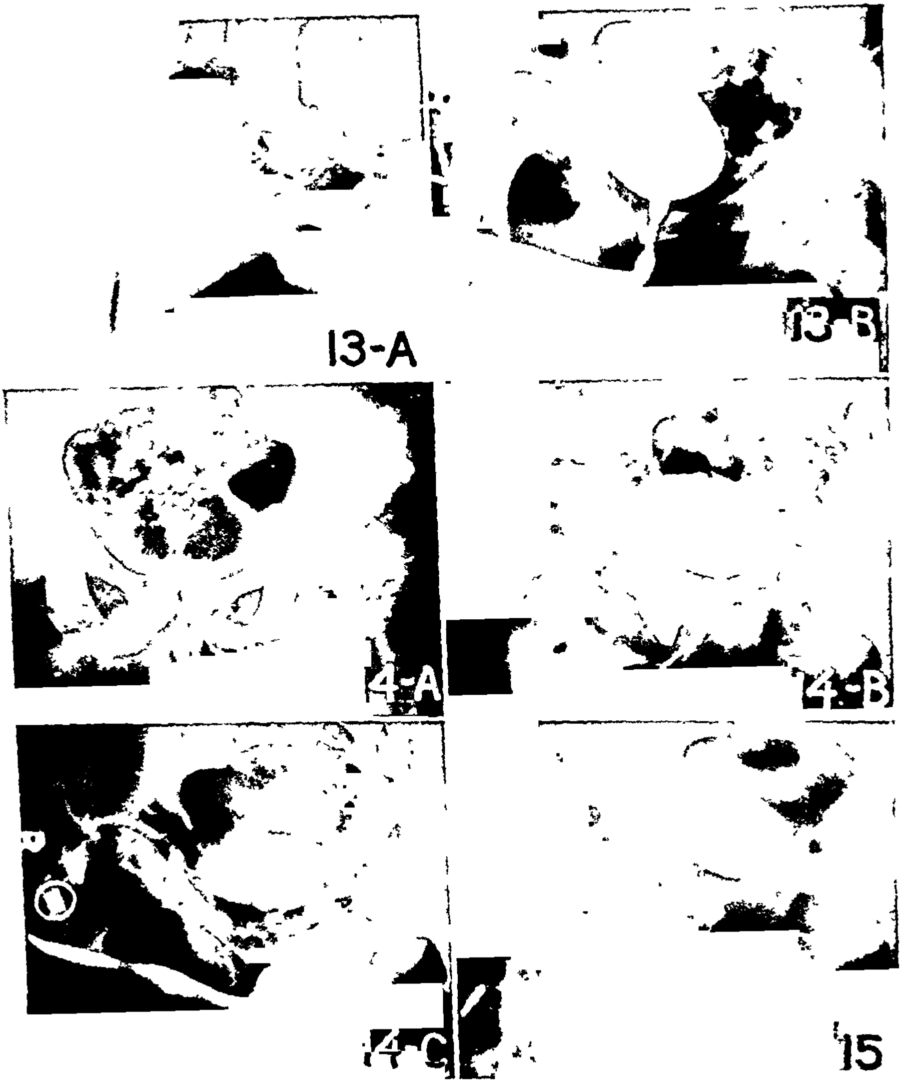

Fig 6 Case 13 (register No 4977), *A*, preoperative; *B*, postoperative. Case 14 (register No 13-121), *A* shows calculus in urethral diverticulum on plain film; *B*, urethrogram; *C*, postoperative film. Case 15 (register No 8322) is preoperative film on paraplegic who died of pulmonary tuberculosis before postoperative film could be obtained, but necropsy showed successful repair of urethra.

support. A slip of rubber dam is left down to the urethra to serve as a drain for 24–48 hours. The 24F Foley catheter is replaced by an 18F soft rubber catheter to act as a splint for 72 hours. A pressure dressing elevates the penis toward the abdominal wall.

Suture materials varied between fine chromic catgut, cotton and combinations of these with fine, stainless steel wire. In 2 of the larger diverticula (cases 1 and 10), cotton suture was used throughout, including closure of the urethra. Only 3 of the operated cases can be said to have healed completely by first intention and in these 3 cases (cases 1, 7 and 9), cotton was the sole suture material used. However, in our experience, the type of suture material was found to influence the end results little if any and more stress should be placed upon such basic surgical concepts as gentle handling of tissues, careful dissection and meticulous attention to hemostasis.

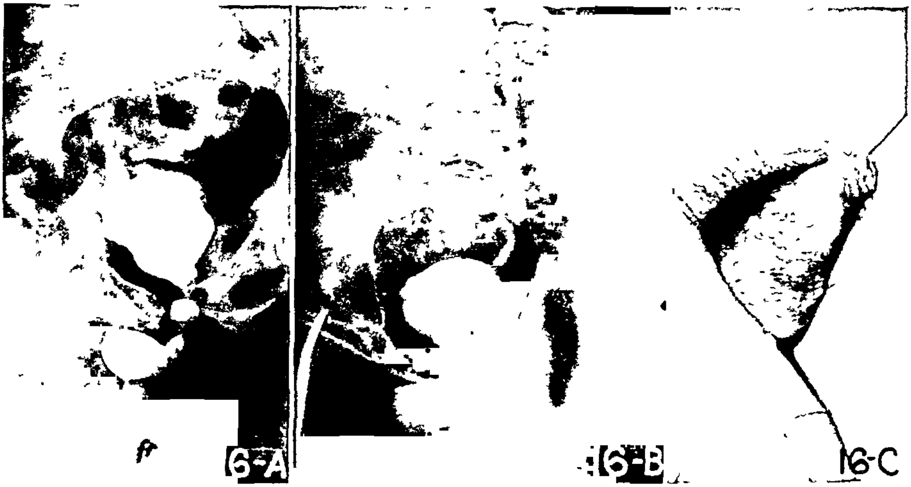

FIG. 7. Case 16 (register No. 506). *A*, urethrogram, May 1947; *B*, urethrogram, April 1948; *C*, photograph April 1948. Patient, wounded February 1, 1944, was maintained constantly on urethral catheter drainage. In January 1946, penoscrotal abscess incised and drained and urethral fistula resulted. Fistula persisted until excised in September 1946. While voiding around cathether in March 1947, patient noted mass size of marble. Diverticulum gradually progressed in size and became chronically infected while vesicoureteral reflux, renal insufficiency and general debility developed. He persistently refused surgical treatment, even diversion of urinary stream. Attempts by patient to keep diverticulum empty by manual expression resulted in severe contusions, so for a short time the expedient of two catheters were tried, one in diverticulum and one in bladder. Finally diverticulum progressed in size to a capacity of 200 cc and then patient would permit catheter in diverticulum only, voiding into sac and urine draining from latter through catheter. Finally on April 23, 1948, permission was granted to perform perineal urethrostomy preparatory to diverticulectomy. While undergoing this form of drainage, patient left hospital against medical advice and his general condition upon return contraindicated surgery. Patient expired on July 20, 1948, and included among post mortem diagnoses were: hydronephrosis, hydro-ureter, bilateral; chronic atrophic pyelonephritis; and generalized amyloidosis.

Infection with drainage from the wound was the cause of greatest concern in the immediate postoperative period. Despite some published reports to the contrary, we have found sterility of the urinary tract in paraplegics a very difficult state to achieve. Already referred to is the fact that only 3 cases healed per primam. However, there were no wide separations of the incisions and in most cases the drainage was of a seropurulent type. Six of the cases drained urine through the operative site at one time or another and 3 of these cases (cases 3, 5 and 6) required surgical excision of an urethral fistula postoperatively. One case (case 4) developed a large hematoma in the operative area after removal of the drain on the second postoperative day and required evacuation of the clots with packing. In general, frequent surgical dresings and a generous amount of patience on the part of both surgeon and patient resulted in satisfactory end results. Streptomycin administered in large doses was found to be very effective in reducing the amount of infection. A single instance of mild postoperative stricture (case 8) responded readily to urethral dilatation.

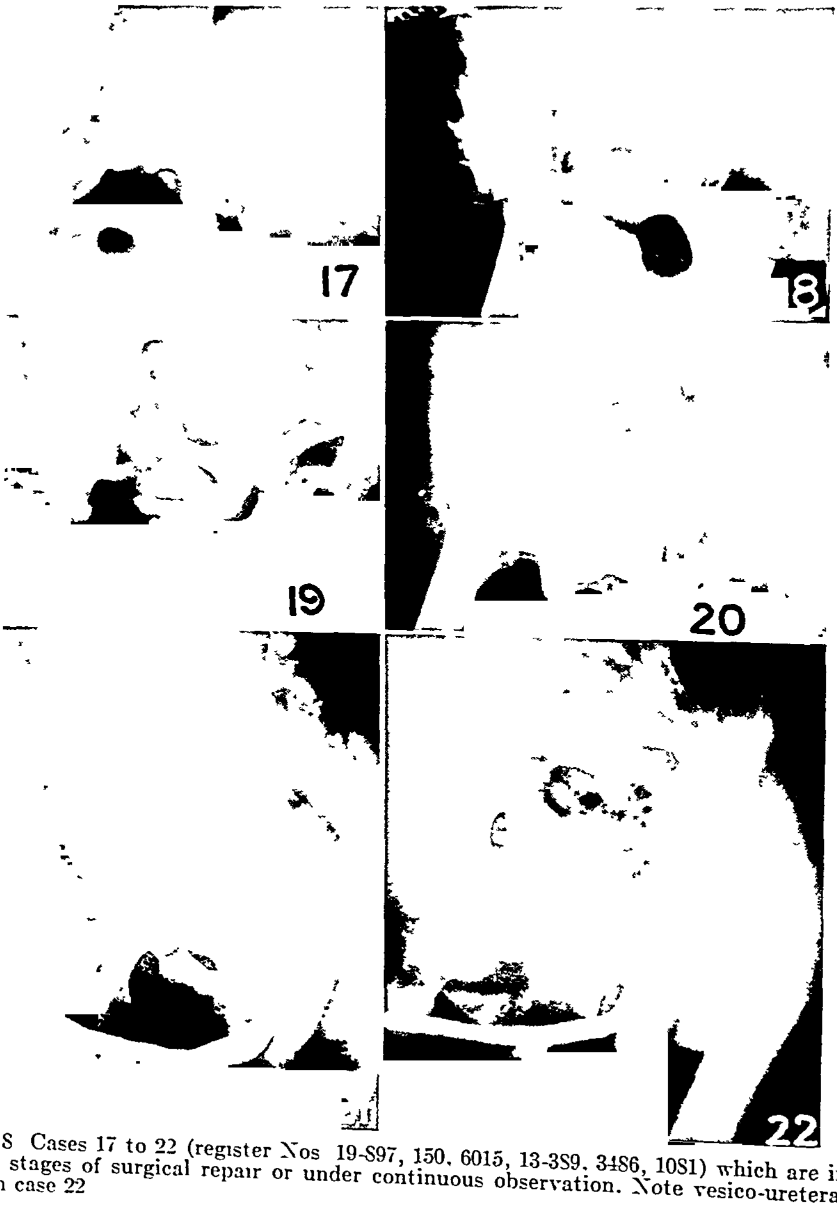

FIG. 8 Cases 17 to 22 (register Nos 19-897, 150, 6015, 13-389, 3486, 1081) which are in varying stages of surgical repair or under continuous observation. Note vesico-ureteral reflux in case 22

Another distressing postoperative complication encountered was failure of the perineal fistulas to close following discontinuance of perineal catheter drainage.

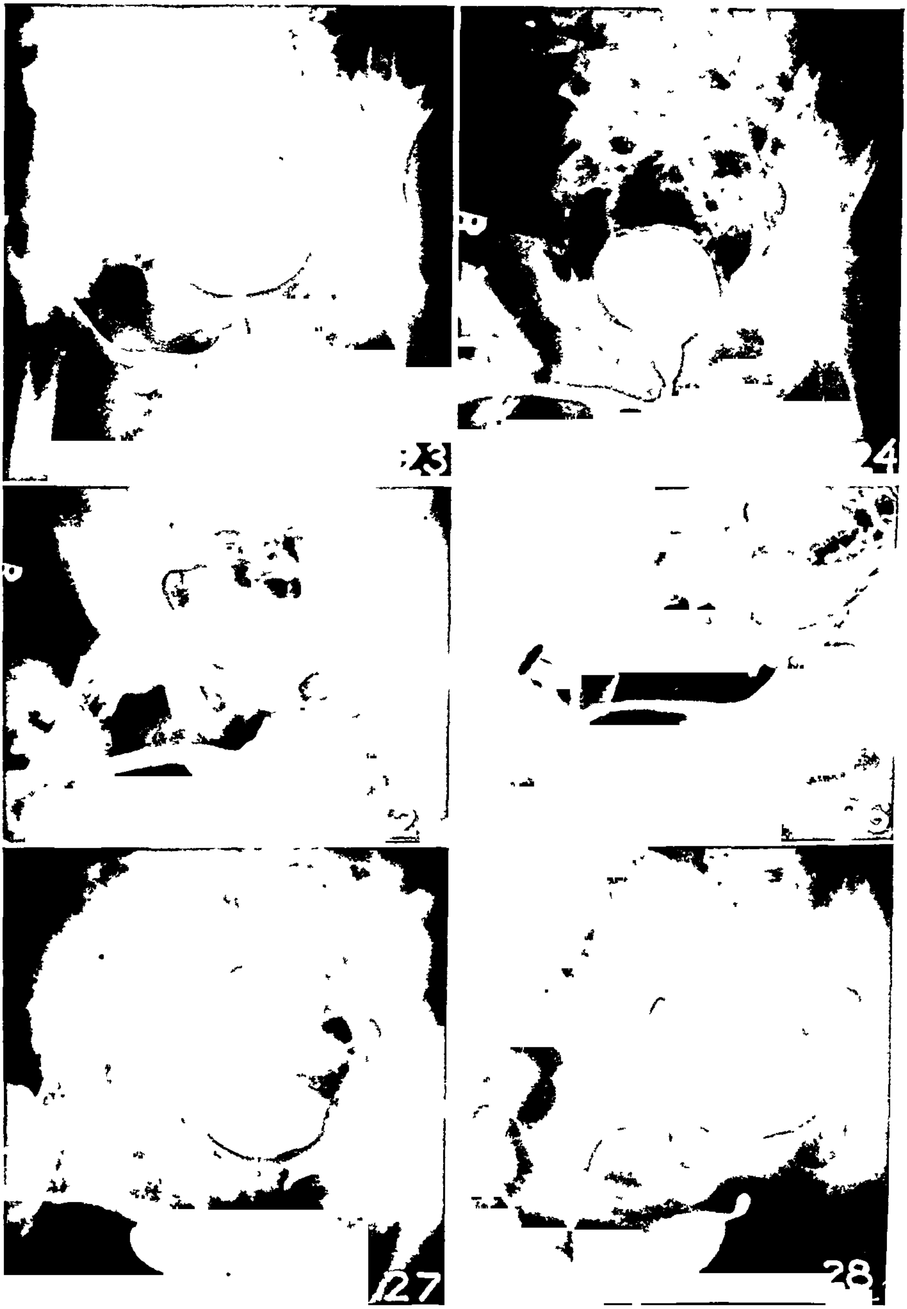

FIG 9. Cases 23 to 28 (register Nos 17-208, 147, 7424, 143, 151, 12-055) in varying stages of surgical repair or under continuous observation. Note vesico-ureteral reflux in cases 23, 24 and 27.

Thirteen of the patients underwent perineal urethrostomy. The long continued presence of the tube and the presence of secondary infection resulted in the formation of a very rigid, fibrotic tract. The reluctance of suprapubic cystostomy tracts in paraplegics to heal spontaneously has previously been reported. In spite of urethral catheter drainage there occurred some leakage of urine through the perineal tract. The proximity of the sinus to the anus coupled with the poorly controlled bowel habits of these patients contributed to infection. Although the tract was curretted and other local treatment instituted, the fistulas failed to heal in a majority of the cases. Therefore a policy of surgical closure was adopted in all cases undergoing perineal urethrostomy. As soon as it was determined that the diverticulectomy wound was well healed, the perineal tract was dissected and the wound closed in layers. Even so, 2 cases required secondary closure of the perineal wound.

Follow-up on these patients includes regular urethroscopic and urethrographic examinations, as well as the usual routine urologic checks given paraplegics. Periodic urethral dilatation is carried out to prevent urethral stricture. Patients are advised against wearing incontinence clamps. A commercial male urinal (Davol No. 19) is probably the most satisfactory if some incontinence device is necessary.

In such an extensive series of cases it is not feasible to report complete case histories. The cases are therefore presented through the medium of photographs of roentgenograms (figs. 2 to 9), and are roughly divided into three groups according to treatment instituted up until the present report: 1) those in which diverticulectomy has been performed, 2) cases in which surgery was recommended but the patients refused, and 3) those cases which are under observation. Although surgical correction of the diverticula so far has been tedious and time consuming, there have been no severe postoperative complications. Operative results, while not spectacular, have been satisfactory and perhaps have lent support toward increased surgical intervention.

The prevention and treatment of this condition is only one link in the unsolved riddle of the proper urologic care for paraplegics. Until personal opinions and impressions give way to scientific facts based upon large statistical studies, many of these patients may not be afforded the best treatment. But such a tremendous consideration is not within the scope of this paper.

Further investigation will be necessary to determine the correlation, if any, of urethral diverticula with upper urinary tract changes, as well as the effect of diverticulectomy in altering the course of such changes. The incidence of recurrence of urethral diverticula also must await the elapse of time and further study.

SUMMARY

The literature has been reviewed and 197 cases of diverticulum of the male urethra have been tabulated as to location and etiology. Forty-five of the cases were found to be acquired diverticula of the anterior urethra. To the latter figure is added 28 cases in paraplegics.

Etiology, pathology, symptoms, diagnosis and treatment with special reference to paraplegics is discussed.

Cases are presented by means of photographs of roentgenograms made on each patient.

We wish to acknowledge the assistance of Mr. John Hancock, chief urologic technician, and Mr. J. E. Billips, medical illustrator.

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REFERENCES

Alcock, N G Tr Am Assoc Genito-Urin Surg , **22:** 293, 1929
Asteriades, T Presse méd , **38:** 632, 1930
von der Becke, A Rev de Especialid, **3:** 736, 1928
Bloch, G Sperimentale, Arch di biol (no 2), **86:** XL, 1932
Bors, E Vet Adm Techn Bull , TB 10 503, December 15, 1948
Bumpus, H C Surg , Gynec and Obst , **29:** 388, 1919
Campbell, M F J Urol , **30:** 113, 1933
Carlton, C H Brit Med J , **1:** 376, 1932
Casini, A Policlinico (sez chir), **43:** 145, 1936
Castro Soc franc d'Urol , pp 158–161, 1926
Chiodin, L and Litmanovich, M Bol Soc de Cir de Rosario, **13:** 33, 1946.
Chwalla, R Wien klin Wchnschr , **44:** 1504, 1931
Clark, J B J A M A , **107:** 31, 1936
Delgado, R Bol Soc de cir de Rosario, **9:** 607, 1942
Dozsa, E Ztschr f urol Chir u Gynak, **44:** 78, 1938
Epstein, G E J d'urol , **25:** 441 1928
Fagerstrom, D P J Urol , **49:** 357, 1943
Frontz, W Tr Am Ass Genito-Urin Surg , **24:** 303, 1931
Galthier, C and Gayet, R J d'urol , **45:** 524, 1938
Geiringer, D and Zuker, M O Am J Surg , **44:** 463, 1939
Huddy, G T B Brit J Surg , **13:** 50, 1925
Irwin, W R Brit J Urol , **4:** 257, 1932
Iverson, E D and Jorgensen, H Lyon chir , **35:** 37 1938
Johnston, F P J Urol , **10:** 295, 1923
Katayama, Y Acta de dermat , **20:** 19, 1932
Kini, M G Brit J Urol , **11:** 155, 1939
Knox, W G J Urol , **58:** 344, 1947
Kolbenheyer, Z Ztschr f urol Chir u Gynak, **45:** 217, 1940
Kretschmer, H L Surg , Gynec and Obst , **62:** 634–640, 1936
Langer, E Ztschr f Urol , **24:** 519, 1930
Lowsley, O S and Gutierrez, R Revista de Med y Cir de la Habana, **33:** 229–298, 1928
Lowsley, O S and Davalos, A Personal communication
LeComte, R M and Herschman, J J J Urol , **30:** 463, 1933
McGavran, H G J A M A , **120:** 1831, 1942
McKay, R W and Colston, J A C Surg , Gynec and Obst , **48:** 51, 1929.
Mitrofanov, P P Vestnik khir , **56:** 118, 1938
Mouatt, T B Brit J Surg , **16:** 51, 1928
Muller, A Arch f klin Chir , **145:** 435, 1927
Neugebauer, F Beitr z klin Chir , **132:** 719, 1924
Nichita, M I Scavenola A and Pascu, C Cluj med , **11:** 136, 1939
Nicholson, B B J Urol , **18:** 145, 1927
Pate, V A and Bunts, R C J Urol , **60:** 915, 1948
de la Pena, A and Hendrick, J A , Jr J Urol , **39:** 678, 1938
Rabinovic, M Vracebnaja gazeta Jg 31, Nr 6, S428 1927 (Russisch)
Repman, H J and Warren, J W J Urol , **59:** 44, 1948
Revoir, J Zentralbl f Chir **64:** 2612, 1937
Rioseco, E and Vargas, J Urol and Cutan Rev , **48:** 209, 1944
Ritter, C and Leidel, G Arch f klin Chir , **164:** 574, 1931
Rocz, A van Adler Ztschr f urol Chir **37:** 213–220 1933
Salleros, J and Vilar, G Rev de Especialid, **3:** 139, 1928
Seymour, G C Canad M A J , **45:** 410–411, 1941
Shafman, S A Khirurgia, No 12, pp 154, 1937
Simon, H Beitr z klin Chir , **145:** 639, 1929
Sisk, I R J Urol , **12:** 169 1924
Sosin, J · Polska gaz lek , **10:** 792–794, 1931
Tagariello, P Riv di Chir , **3:** 537, 1937
Tavares, A , Moreno, O and Pereira, S Med Contemp , **47:** 333, 1929

TEDENAT AND SINNESEAL, A.: Progres med., **42**: 1924, 1927.
TEMPORAL, A.: Arq. brasil. de Cir. e Ortop., **8**: 88, 1940.
TERNOVSKY, S.: Urol. and Cut. Rev., **34**: 578, 1930.
TRAFTON, H. M.: S. Clin. North Amer., **25**: 589, 1945.
WATTS, S. H.: Johns Hopkins Hosp. Rep., **13**: 49, 1906.
WAUGH, J. R.: J. Urol., **28**: 619, 1932.
YOUNG, H. H. AND SHAW, E. C.: South M. J., **19**: 42, 1926.
ZIDE, H. A. AND SIEGEL, M. S.: Calif. Med., **65**: 279, 1946.

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CHOLESTEATOMA OF THE EPIDIDYMIS

LOUIS J. PINGREE AND DONALD E. BROWN

In 1946 Kundert briefly discussed the structure and classification of an unusual type of tumor that has been designated as cholesteatoma. He reported an instance of such a growth in the epididymis, and on reviewing the literature on epididymal tumors he was unable to find any previous report of such an occurrence. Because of the evident rarity of cholesteatoma of the epididymis, we believe that we are justified in reporting this second case.

CASE REPORT

M. C. C., a white man 55 years old, was examined because of an asymptomatic, hard, nodular mass involving the upper pole of the right epididymis, which had been present 15 years. Twenty-five years ago the scrotum had been bruised but not enough to break the skin. No history of testicular infection was obtained.

Examination revealed a hard, nodular, painless mass which on palpation appeared to involve the entire upper pole of the right epididymis and a small portion of the testicle and extended up the cord about one cm. It measured 3 cm. in length and 2 cm. in diameter and did not transilluminate. Blood cholesterol was 285, the normal for our laboratory being 180.

This grossly resembled a tuberculous process. Due to the involvement of the cord a routine orchiectomy was done. The patient left the hospital 5 days later and has not been seen since.

Pathological report. (Dr. D. E. Brown): "The gross specimen reveals the caput of the epididymis to be very firm in consistency and on cut section demonstrates scattered yellowish brown areas (fig. 1).

"The microscopic examination revealed a normal epididymis except for the caput (fig. 2). Here the section is composed of moderately dense connective tissue. Scattered throughout this connective tissue are ovoid areas with a somewhat undulating contour composed almost entirely of densely hyalinized collagenous bundles. Here and there are small areas measuring approximately ½ a low power field in diameter composed of densely basophilic granular material, presumably representing calcium. An occasional stellate shaped duct lined with a low cuboidal type epithelium is noted. This probably represents some portion of the rete. Also present are ovoid areas measuring ½ to 1½ low power fields in diameter and containing innumerable needle-shaped clefts. The appearance of these clefts is pathognomonic of the presence of cholesterol and cholesterol esters which have been dissolved out in the process of preparation. Examination of frozen sections under polarized light reveals this material to be highly birefringent. In some of these areas the cholesterol crystals are surrounded only by a relatively amorphous densely hyalinized collagenous tissue. In others a fairly marked cellular reaction is present and in immediate anatomical juxtaposition to the crystals are large numbers of multinucleated giant cells. Here and there the interstitial tissue demonstrates a sparse sprinkling of lymphocytes but cellular infiltration is not a prominent feature.

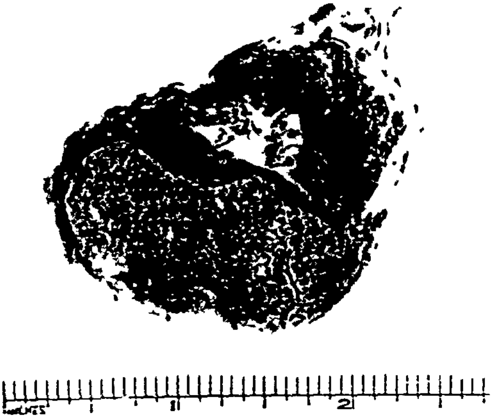

FIG. 1

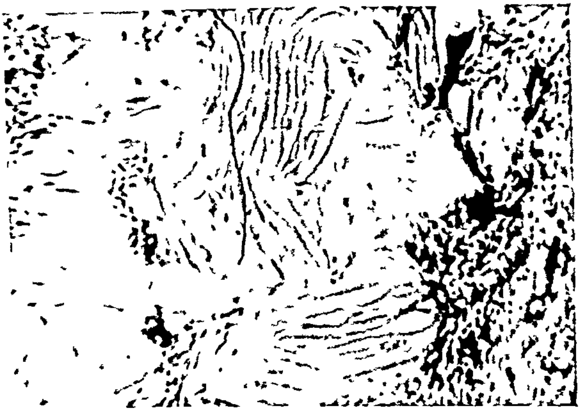

FIG. 2

DISCUSSION

Our case is similar to the original one. It would have been interesting to have investigated our patient further regarding his elevated cholesterol. Kundert explored the various etiological factors involved in the production of these lesions and further discussion of this would be repetitious.

CONCLUSION

The second case of cholesteatoma of the epididymis is reported.

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REFERENCE

KUNDERT P. R : J. Urol , 56: 454–457, 1946.

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TREATMENT OF MALIGNANT TUMORS OF THE TESTIS

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This study was undertaken to determine the comparative efficacy of the usual methods of treating tumors of the testis, i. e. simple orchiectomy followed by radiation therapy as opposed to radical surgery and radiation.

Soon after the survey was begun, the authors realized that none of the large number of pathological classifications of tumors of the testis seemed entirely adequate for such a comparative analysis. Friedman and Moore's new classification was used not only because it more closely predicted the behavior of any given testicular tumor but also because it had been used by Lewis in his large series of cases treated by radical surgery and radiation. This study is, therefore, essentially a comparison of results obtained in our series of testicular tumors treated at the University of Virginia Hospital by simple excision and radiation and Lewis' series treated by excision of the tumor and radical dissection of regional lymph nodes followed by radiation.

We found in our series, as did Friedman and Moore, that the great majority of tumors fell into four main groups: seminoma, embryonal carcinoma, teratoma and teratocarcinoma appearing singly and in combination. There was, in addition, a fifth miscellaneous group in which Friedman and Moore placed tumors not falling in this category. This latter group made up only 4 per cent of their tumors but comprised 13 per cent of ours.

Seminomas are monocellular type of tumors usually composed of round or polyhedral shaped cells having a fairly large nucleus in which the nucleolus is centrally located. The cytoplasm is clear, the border distinct. The cells are uniform and distributed in sheets or masses in a rather monotonous fashion. Some of these tumors are atypical in that the cells are more malignant as evidenced by marked anaplasia (fig. 1).

Embryonal carcinomas present a wide variation in their structure. Frequently encountered types in the same tumor are adenocarcinoma, papillary adenocarcinoma or undifferentiated carcinoma (figs. 2 and 3, *A*). Others show cytotrophoblastic tissue, while still others show the usual picture of chorio-epithelioma (fig. 3, *B*). The embryonal carcinomas in general show a greater degree of malignancy microscopically than is seen in the seminomas.

Teratomas are derived from more than one primitive germ layer. They are cystic and solid tumors which histologically are composed of adult tissue and show no evidence of malignancy. Friedman and Moore have shown that these histologically benign appearing tumors are capable of metastases and are potentially malignant.

Teratocarcinomas are tumors showing histologically malignant tissue in association with teratoid elements. The malignant cells may be seminoma or embryonal carcinoma. Malignant changes can also take place within the teratoid structures themselves (figs. 4 and 5).

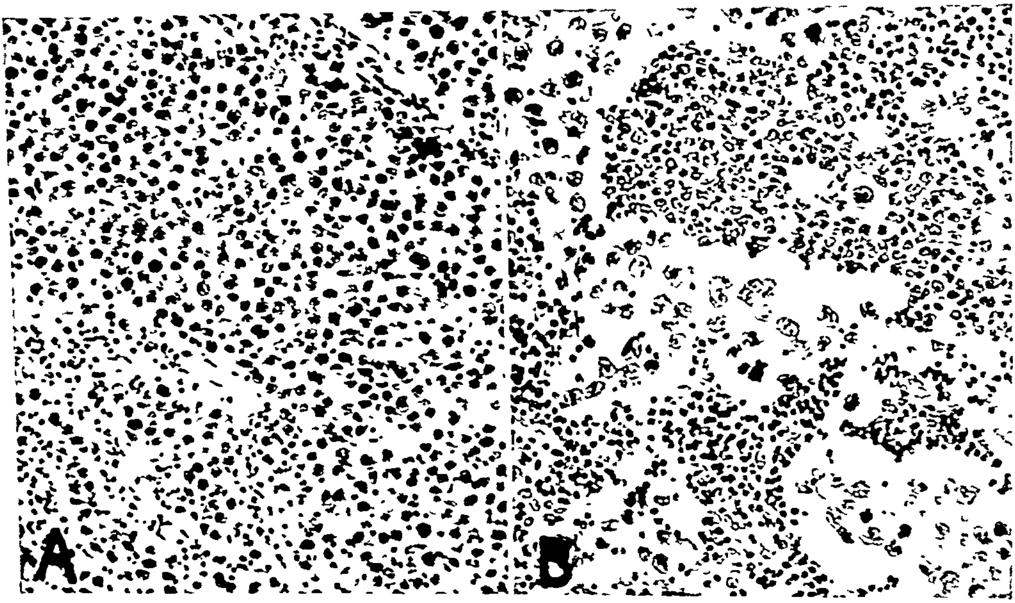

FIG. 1. *A*, typical seminoma *B*, atypical seminoma Note greater variation in size and shape of cells with an increased number of mitoses.

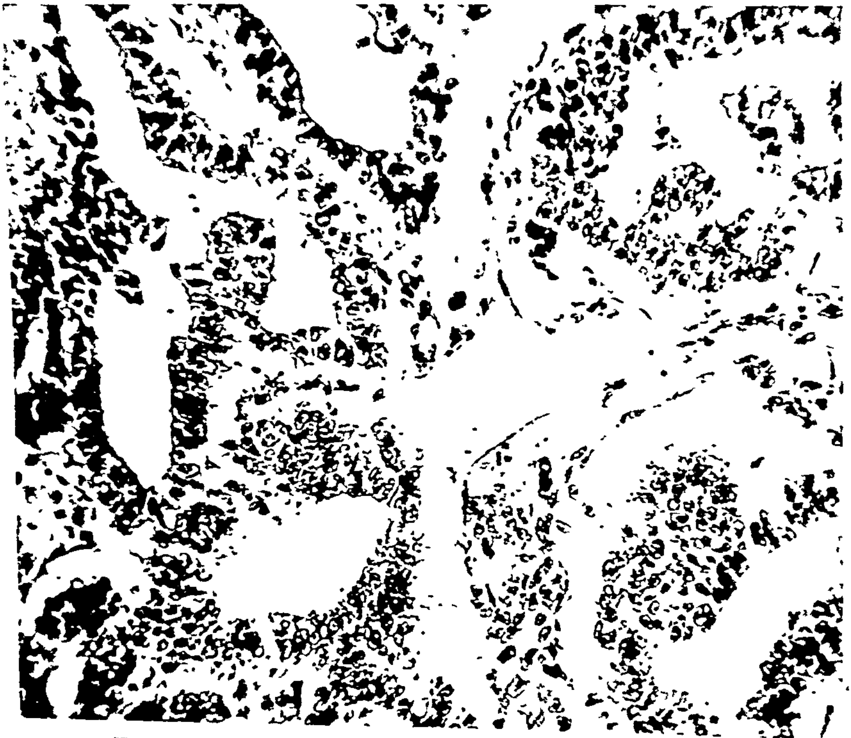

FIG. 2. Embryonal carcinoma. Shows typical adenocarcinoma

The diagnosis of tumors composed of more than one element is the diagnosis of the most malignant element. Lewis points out that the type of neoplastic cell must be clearly defined in order to predict the eventual behavior of the tumor.

Our material was collected from the Departments of Urology and Pathology of the University of Virginia Hospital and includes all of the testicular tumors seen here over the period 1921–1949. Sixty-seven cases were studied histologically, of which in only 41 were we able to collect clinical and follow-up data.

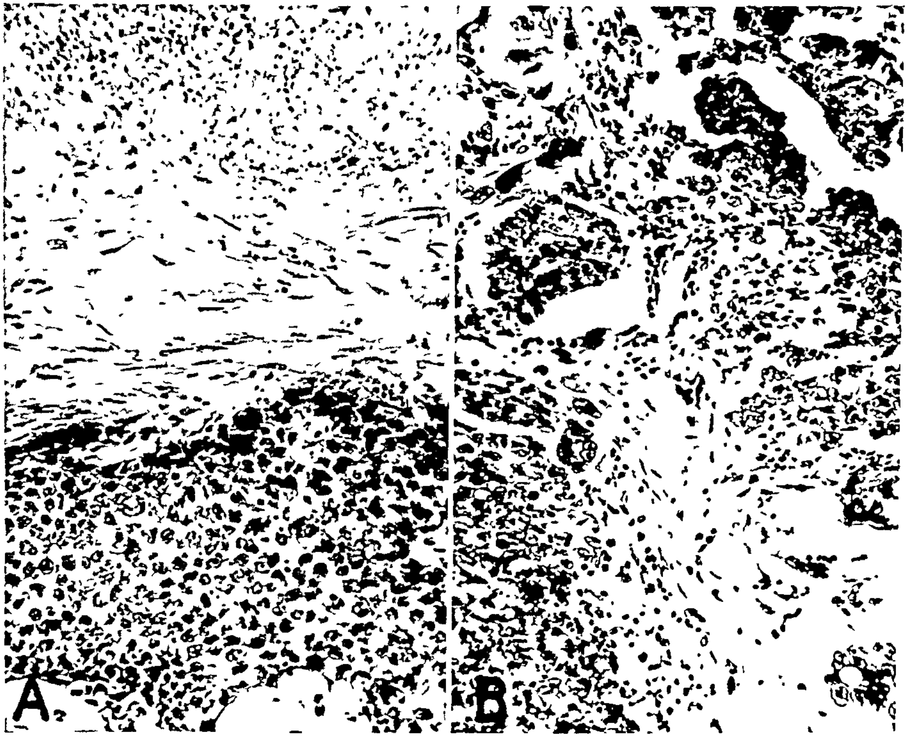

FIG 3. *A*, embryonal carcinoma; undifferentiated type showing adjacent area of necrosis, typical in this tumor. *B*, chorio-epithelioma; a variant of embryonal carcinoma showing synchtial (large multinuclear) and cytotrophoblastic cells.

A classification of the entire series based on Friedman and Moore's work is given in table 1.

More significant is an analysis of the 41 cases upon which follow-up histories were obtained. All of these cases were treated with simple orchiectomies, and most of them received postoperative radiation. The presenting symptom was almost invariably a painless scrotal mass, most frequently (63 per cent) on the right side. Despite a large local Negro population, only 2 (or 3 per cent) occurred in this race. Two of the tumors, both seminomas, appeared in undescended testes. The duration of symptoms varied from 2 weeks to 10 years, the length of time in general being inversely proportional to the degree of malignancy. Friedman and A-Z tests for the gonadotrophic hormone were performed on many of

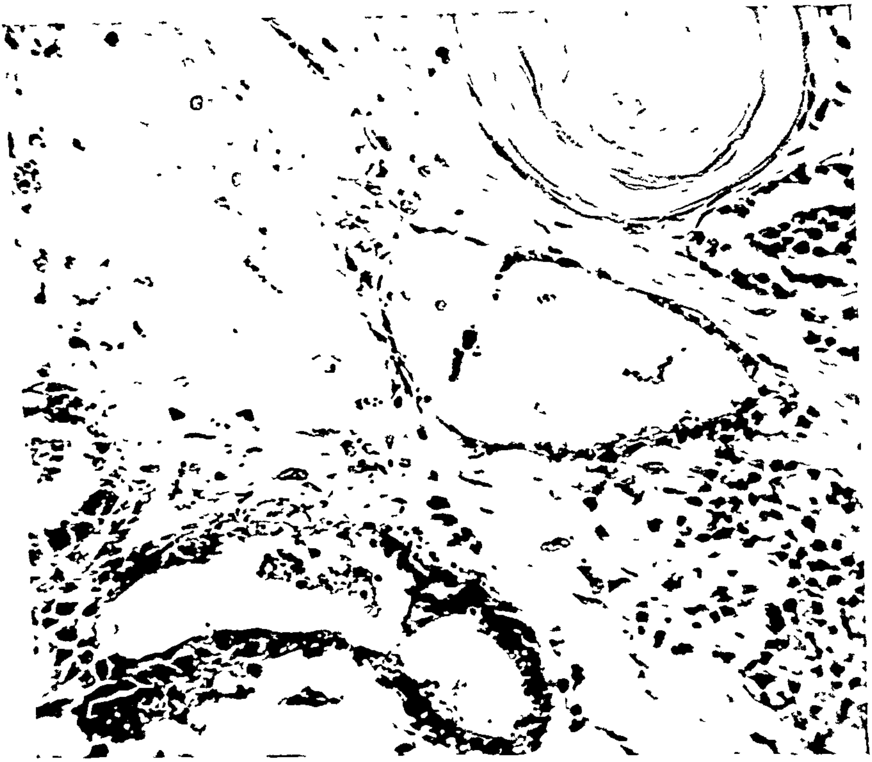

FIG. 4. Teratocarcinoma Shows undifferentiated carcinoma, adenocarcinoma and squamous epithelial elements

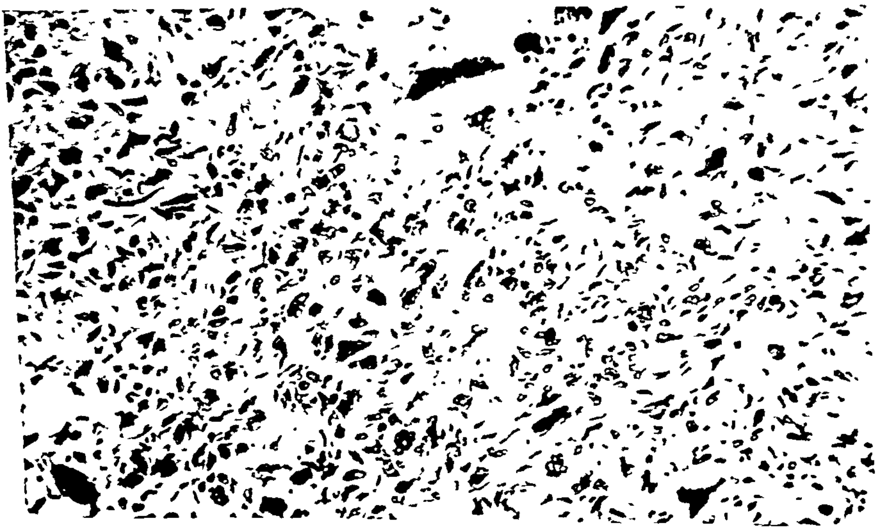

FIG. 5. Rhabdomyosarcoma. Note multinucleated cells, which show striations under higher magnification.

these cases. Positive tests were found in over 50 per cent of the embryonal carcinomas tested. Of the seminomas tested, only 2 were positive, these being of the equivocal or anaplastic type.

A striking feature was the wide variation in age of these patients with testicular tumors. The youngest was 18 (adult teratoma) and the oldest 78 years (sarcoma). Table 2 shows the average age, the median age and the age range. Only seminomas and embryonal carcinomas occurred in our series with enough frequency to make them adequate for analysis.

TABLE 1. *Pathological classification*

	UNIV. OF VA. SERIES		FRIEDMAN AND MOORE SERIES, %
	No.	%	
Seminoma	27	40%	35%
Embryonal carcinoma	20	30%	19%
Teratocarcinoma	9	13.5%	35%
Teratoma	1	1.5%	7%
Miscellaneous:			
Sarcoma	5	7.5%	
Lymphoma	2	3%	
Midline scrotal carcinoma	1	1.5%	
Nephrogenic tumor	1	1.5%	
Endothelioma	1	1.5%	
Total miscellaneous	10	13.5%	5%
Total	67		

TABLE 2

	AVERAGE AGE	MEDIAN AGE	AGE RANGE
Seminoma	41 yrs.	35 yrs.	27–70 yrs
Embryonal carcinoma	33 yrs.	33 yrs.	19–50 yrs

These figures suggest that tumors of the testis are not primarily a disease of the young. Both tumors, in our series, occur most often in the fourth decade of life with seminomas appearing as late as the seventh or eighth decades.

A study of table 3 reveals that seminomas offer a better prognosis than other malignant tumors. The prognosis in seminoma usually is in accord with its histological appearance, but some of these tumors are unpredictable with some patients having metastases on admission showing a better survival time than others without metastases. The survival period in some of our cases of seminomas has been long, and 1 patient has lived 19½ years. One case was of particular interest. The patient was admitted without metastases following which a left orchiectomy was performed for seminoma. Seventeen years later he developed a seminoma in the remaining testicle. A right orchiectomy was performed and the patient died 4½ years after this second tumor of coronary occlusion without evidence of metastatic recurrence of the seminoma. With the relatively high survival rate in the case of seminomas and the known radio-sensitivity there is no dissention concerning the treatment of this tumor. All urologists agree that simple orchiectomy plus extensive radiation therapy is the treatment of choice. Lewis has also abandoned radical gland dissection for these tumors after 60 operative cases.

The remaining types of tumors in this series, with the exception of embryonal carcinomas, are too small in number to evaluate. Although both of our cases of teratocarcinomas are living, there is no reason to expect these tumors to behave any differently than their most malignant elements. Several of the miscellaneous tumors, mainly the two lymphomas, one of the sarcomas, and a midline scrotal carcinoma, are possibly secondary in the testes. They are included here because no primary extratesticular site was found.

TABLE 3. *Results of treatment: Simple orchiectomy plus x-ray treatment*

TUMOR	NO.	WITH METASTASIS ON ADMISSION	LIVING	DIED	NOT FOLLOWED
Seminoma	12	3—(25%)	8—(67%)	3—(25%)	1—9%
Embryonal carcinoma	15	7—(17%)	8—(53%)	6—(40%)	1—7%
Chorio-epithelioma	2	2—(100%)	0—	2—(100%)	0—
Teratocarcinoma—(3)	2	0—	2—(100%)	0—	0—
Rhabdomyosarcoma	1	1—(100%)	0—	1—(100%)	0—
Teratoma	1	0—	1—(100%)	0—	0—
Miscellaneous	(8)				
Lymphoma	2				0—
Sarcoma	3	1—(33%)	0—	3—(100%)	0—
Midline carcinoma	1	0—	0—	0—	1—
Endothelioma	1	0—	1—(100%)	0—	0—
Nephrogenic tumor	1	0—	1—(100%)	0—	0—

TABLE 4. *Cure rate of embryonal carcinoma (exclusive of chorio-epithelioma)*

ORCHIECTOMY AND RADIATION	ORCHIECTOMY, RADIATION AND RADICAL GLAND RESECTION (LEWIS)
15 cases 53% survival (1 not followed)	45 cases 33% survival (5 not followed)
Followed 2-23 years	Followed 1½-5 years

The object of this study concerns the treatment of embryonal carcinomas. These tumors follow their histological pattern in that they behave in a more malignant manner. Those with chorio-epitheliomas have a uniformly fatal prognosis. With the exclusion of two cases of embryonal carcinoma having chorio-epithelioma, it can be noted in table 3 that of our 15 cases of embryonal carthese cases. Positive tests were found in over 50 per cent of the embryonal carcinomas tested. Of the seminomas tested, only 2 were positive, these being of the equivocal or anaplastic type.

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We wish to express our appreciation to the section of urology at the Army Institute of Pathology for their aid in the proper pathological classification of our cases according to Friedman and Moore.

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REFERENCES

Friedman, N. B. and Moore, R. A.: Tumors of the testis. Military Surg., **99:** 573, 1946.
Lewis, L. G.: Tumors of testis. J. Urol., **59:** 763, 1948.
Lewis, L. G.: Radical orchiectomy for tumors of the testis. J. A. M. A., **137:** 828, 1948.

cinoma, 53 per cent survived 2 to 23 years. One patient could not be followed beyond $2\frac{1}{2}$ years and is assumed to be dead. Of interest is the fact that 2 of the patients when first seen had pulmonary metastases. Both are living 4 and 7 years later; the former, following orchiectomy and radiation therapy alone, and the latter following radiation therapy and lobectomy. Neither case shows demonstrable metastases at this time. Our survival rate of 53 per cent is indicative of the effectiveness of the treatment of these tumors by orchiectomy and x-ray. It is in this group that the question of treatment is of considerable interest to the urological profession. Lewis has reported his results in 45 cases following radical gland dissection and radiation therapy. The results of other authors cannot be used for comparison because of the lack of a common classification such as the Friedman-Moore. The cure rate in Lewis' series is compared with ours as shown in table 4.

These two series on results of treatment of embryonal carcinomas are comparable because the classification of Friedman and Moore was followed in each instance. Lewis has reported a cure rate of 33 per cent following radical surgery in 45 cases of which he was able to follow 40. It is possible that Lewis was dealing with a more malignant tumor in a younger age group, although there are no differences from a histological standpoint. The median age in our cases was only 33 years with a range of 19 to 50 years. If the results in these two series are comparable, it would seem that as far as civilian practice is concerned the necessity of radical gland dissection for the treatment of embryonal carcinoma is not proven. A study of the 2 cases of embryonal carcinoma with pulmonary metastases previously described would lead us to believe that some of these tumors are more radio-sensitive than Lewis and Friedman have indicated. It would appear unnecessary to use intensive postoperative x-ray therapy if these tumors are really radio-resistant. It is possible that the number of cases in each series is not statistically sufficient upon which to base either method of treatment. The lack of superiority in Lewis' radical surgery series may be that his surgery is not radical enough, and that the glands above the renal vessels should also be removed. The latter is being advocated and performed by Wyland Leadbetter.

CONCLUSION

The proper therapy for embryonal carcinoma of the testes have not yet been determined. The additional value of gland dissection, as advocated by Lewis, is problematical because all of his 40 cases *in addition* received therapeutic radiation with a million volt machine. We conclude that in order for proper therapy to be determined in embryonal carcinoma, it is important for urologists in other clinics to reclassify their testicular tumors according to Friedman and Moore and report their results in the treatment of embryonal carcinoma. From the study of our cases one arrives at the tentative assumption that simple orchiectomy plus radiation therapy of 200,000 volts is as adequate as orchiectomy with radical gland dissection plus radiation therapy with a million volt machine. A conclusive answer to this problem is not simple and a certain number of emratio 3.1/3.5 per cent; Wassermann negative. A chest film showed fibrous strands and mottled areas in both summits consistent with partially fibrotic and partially productive tuberculosis, with a trachea deviated mildly to the right. There was thickening of the medio-trunk shadows consistent with chronic pneumonitis or passive congestion. The abdominal film, excretory urogram, the cystoscopic findings, repeated urinary studies for tuberculosis, and electrocardiogram were negative.

A diagnosis of chronic epididymitis and funiculitis, possibly tuberculosis, was made. An exploratory operation was done. The testicle and attached cord were easily delivered through a small incision, and the testicle appeared to be normal. The cord was firm, enlarged to two to three times its normal size, and was confluent with the upper pole of the epididymis. The lower pole was normal in appearance, but nodular to palpation. The testicle, epididymis, and cord to the region of the external ring were removed as a biopsy; the thought being that this was a typical type of tuberculous infection. With a diagnosis of mesothelioma of the spermatic cord, the remaining portion of the tumor was removed. This was found to extend from the external inguinal ring to the peritoneum at the internal ring. At this point, the tumor appeared to fade out although a moderate number of adhesions were present between the lower end of the cecum and this portion of the peritoneum. The appendix was normal and the vas continued retroperitoneally in a normal manner. A large amount of mucoid material was noted about the tumor which was not noted at the time of the first operation.

For 7 days the temperature ranged from 100 to 101F. and the incision drained a moderate amount of mucoid material. By the eleventh day the incision was healed and the patient was ambulatory and eating well. On the thirteenth day he complained of shortness of breath and examination revealed an enlarged liver and mild pitting edema of the extremities. The temperature, pulse, and respiration were normal; the albumin globulin ratio 2.9/3.8 per cent; the electrocardiogram and chest films showed no change from the previous reading. He was placed on a highly supportive regimen, including plasma and blood transfusions, but failed to respond and died on the thirty-fourth postoperative day. Unfortunately no autopsy could be obtained.

The tissues removed (fig. 1) were studied by Drs. A. E. Keasbey and E. Feder, who reported that the first specimen consisted of a testis together with its epididymis and a greatly thickened portion of spermatic cord. The spermatic cord measured 55 cm. in length and in the cut end it measured 2.5 by 2 cm. On its cut surface, the spermatic cord, the blood vessels and vas could be identified. The entire structure appeared quite fibrotic. The tunica vaginalis became obliterated 2 cm. from the distal end of the cord. The cord was indurated, elastic, smooth, but with absence of nodules. On cross section, the knife grated, and a small amount of clear, rather gelatinous material appeared on the surface. No abscesses were encountered. No areas of calcification or necrosis were noted. The surface appeared gray-white and with a few areas of bright yellow material that appeared like interspersed fat. After stripping a very adherent tunic away, the cord measured 7 cm. long and 1.2 cm. at its greatest diameter. The epididymis

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TUMORS OF THE SPERMATIC CORD

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Primary and secondary tumors of the spermatic cord are rare enough so that their occurrence deserves reporting. Since first reported in 1819 by Cloquet, approximately 260 cases have appeared in the literature. Thompson, who reviewed the literature in 1936, states that about 70 per cent of the tumors have been benign; primarily lipomas and fibromas, while 30 per cent have been reported mainly as some type of sarcoma. Strong in 1942, found 257 tumors of the spermatic cord in the literature of which 36 per cent were malignant. In the same year Prince found 74 malignant tumors of the spermatic cord reported in the literature and added 1 case of his own. In 1944, Shivers reported a case of rhabdomyosarcoma of the spermatic cord invading the testicle and epididymis bringing the total number of malignant tumors of the cord to 76 cases.

We wish to report 2 cases of tumor of the spermatic cord. The first is a mesothelioma. These tumors have been reported in the pleural and other body cavities lined by mesothelium, but none had been reported as involving the male genital tract until 1943. In that year, Newton Evans reported 5 cases of mesothelioma of the epididymis and tunica vaginalis and assembled 8 others from the literature. These latter cases were reported by various authors as adenoma, adenocarcinoma, lymph angioma and cavernous lymph angioma. Evans considered that this tumor was benign while Thompson reported 3 of the above 8 cases as adenocarcinoma. In our case the tumor was not encapsulated, appeared to invade the peritoneum, and had the characteristics of a malignant tumor.

It was not possible to determine the point of origin of the tumor in this case. Our first case was taken from the surgical service, Department of Urology, University of Southern California Medical School. A 69 year old white man complained of a painless swelling in the right inguinal area for 15 months. During this time he wore a truss, thinking that he had a hernia. He had no intestinal or urological complaints.

Examination revealed a few scattered, fine rales over the posterior-inferior lung fields. In the right inguinal area, a firm, slightly tender, slightly movable, fusiform tumor mass was felt in the position of the spermatic cord. This tumor measured about 4 cm. in diameter and extended from the region of the external ring to the epididymis. The right testicle was normal in size, shape and consistency; the epididymis was easily palpated and was found firm with some tenderness and nodularity over its lower pole. There was no cough impulse at the inguinal rings, nor was there any lymphadenopathy or abnormal findings noted in the extremities. The rectal examination was negative.

Mild anemia was present; the urine was negative; the nonprotein nitrogen was 38 mg. per cent; phenosulfonphthalein output was 65 per cent in 1 hour with an appearance time of 5 minutes; acid phosphatase 2.2 units; albumin globulin ratio 3.1/3.5 per cent; Wassermann negative. A chest film showed fibrous strands and mottled areas in both summits consistent with partially fibrotic and partially productive tuberculosis, with a trachea deviated mildly to the right. There was thickening of the medio-trunk shadows consistent with chronic pneumonitis or passive congestion. The abdominal film, excretory urogram, the cystoscopic findings, repeated urinary studies for tuberculosis, and electrocardiogram were negative.

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The second specimen consisted of the abdominal end of the spermatic cord, which measured 13 cm. in length and 3.5 cm. in its greatest diameter. The proximal severed end contained suture material and was partially covered by fibrous adhesions. The cord was increased in diameter for a distance of 5 cm. from the proximal end. Distal to this area of thickening it was of normal size and consistency. A small amount of peritoneum could be recognized attached approximately 1.5 cm. distal to the end of the area of thickening. This peritoneum was thickened, injected, and somewhat roughened. The thickened area was covered by fibrous adhesions, felt indurated, and on section showed an infiltration with semi-translucent tissue from which sticky mucoid material could be scraped.

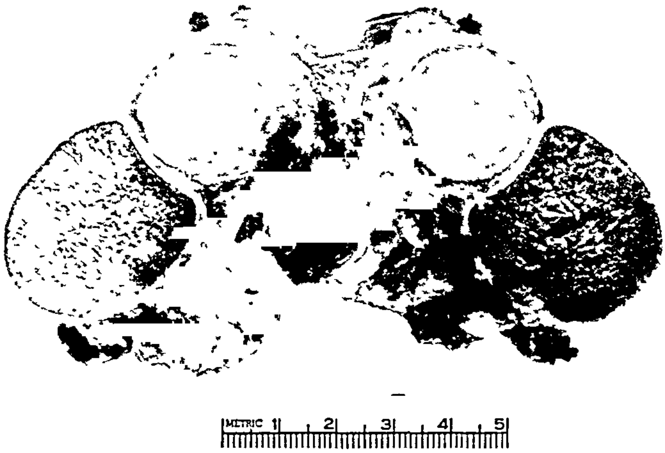

FIG. 1 Gross specimen of mesothelioma of cord with normal testis

The microscopic sections showed sheets and strands of small hyperchromatic cells in a dense fibrous stroma which formed irregular spaces lined by flattened cells with bulging nuclei, some of which appeared dilated. The spaces contained mucus-like material and desquamated tumor cells. A moderate number of mitotic figures were present. The diagnosis was mesothelioma, spermatic cord with extension to the peritoneum. See figure 2, *A*.

The second case is one of teratoma involving the testicle, epididymis, and spermatic cord. The primary site could not be determined, although it was assumed that it was in the testis with infiltration into the epididymis and spermatic cord. To our knowledge, no similar case has been reported. A white man, aged 38, was referred to me because of a swelling on the left side of the scrotum, first noticed 4 months previously and consistently grew larger. For the last 2 weeks he had had aching pains in the left scrotum that radiated up to the left lower quadrant.

Examination of the left scrotum revealed a moderate sized mass, fluctuant and not hard. Light was transmitted around the periphery, not through the center. The cord was felt as a large firm mass extending up beyond the external ring and along the inguinal canal. This was very hard and about 4 cm. in diameter. The epididymis could not be outlined.

The prostate was normal to palpation; the left seminal vesicle was not enlarged, neither was the right. The genito-urinary examination otherwise was normal. No masses could be felt in the abdomen. X-rays of the chest and pelvis were negative.

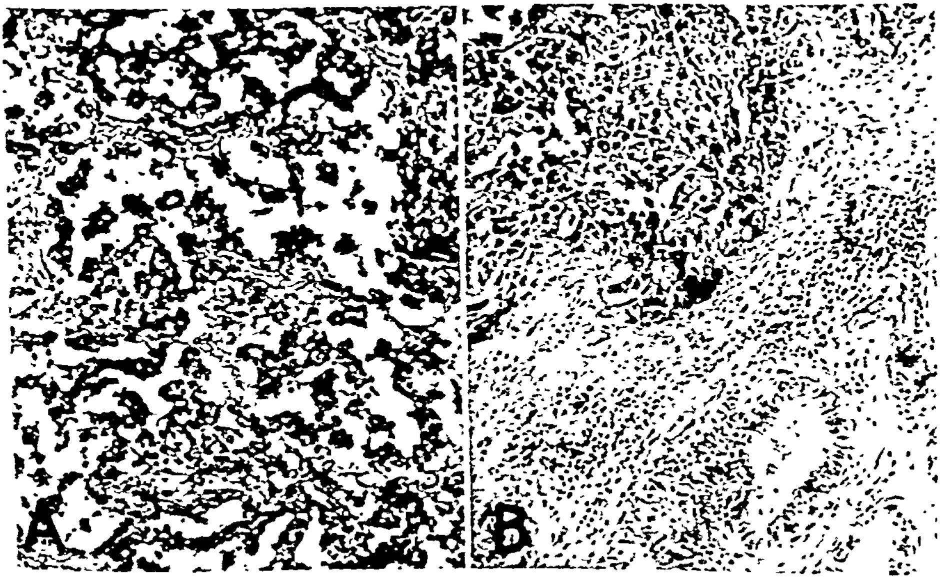

FIG 2. A, mesothelioma of cord. *B*, teratoma of cord

A diagnosis of hydrocele with possible tumor of the testis was made. It was believed that the mass along the cord was either hydrocele or tumor mass. Prolan A was not done.

On June 7, 1946, the scrotum was opened and about 60 cc clear, straw colored fluid removed. The testis and epididymis were enlarged and very firm. The cord was very firm and solid and about 4 cm. in diameter. The scrotal incision was carried up along the canal to the internal ring. The mass extended beyond the internal ring. With the finger in the ring, the thickened, hard cord could be felt curving posteriorly.

It was believed that the mass could not be removed entirely with a reasonable hope of cure. For this reason the cord was resected at the internal ring and the testis, epididymis, and cord removed in one mass. The wound was closed.

The patient left the hospital in 4 days but continued to have the pain of which he previously had complained. He was referred to the Los Angeles General Hospital for x-ray therapy, but his step-father referred him to an osteopath. The patient went rapidly downhill and died about 3½ months following operation. No autopsy was done.

The pathological report was made by Dr. George Maynor at the Good Samaritan Hospital. The specimen consisted of testicle, epididymis, and part of the spermatic cord. The testicle was slightly enlarged, firm and leathery in consistency but faintly nodular. It measured 6½ cm. from pole to pole with maximum thickness of 4 cm. The tunica albuginea was thickened, wrinkled, scarred, and presented several small, slightly elevated firm, gray-white areas. On sectioning, the parenchyma presented a yellow-gray mottled appearance with practically all of the parenchyma being replaced. Visible throughout the section surface were several dull, yellow, map like areas of necrosis.

The epididymis was thickened to about 1 cm., nodular, firm, and adherent to the testis. Multiple sections revealed nodular, gray and yellow-gray areas.

Approximately 8 cm segment of spermatic funiculus was attached. This was greatly thickened, firm, stiffened and nodular. It had an average diameter of 3 cm. Sections show a replacement with yellow and yellow-gray tissue.

The microscopic section of the testis showed a malignant teratoma with carcinomatous elements predominating. These areas were made up of large compact masses and sheets of large, irregular, round or polyhedral shaped cells with large vesicular or oval nuclei containing single prominent nucleoli as a rule. Cell borders were poorly defined and cytoplasm was opaque. Many nuclei were in mitotic division. At some points the pattern was that of an embryonal adenocarcinoma. In one or two areas the cell type and arrangement was that of a seminoma. Necrosis was a prominent feature in all sections. Infiltration extended into the epididymis and the spermatic funiculus even up to the upper margin of resection. See figure 2, *B*.

The diagnosis was malignant teratoma of testis with infiltration into the epididymis and spermatic funiculus.

These cases are presented not only because of their rarity, but because they present a problem in the differential diagnosis of swelling in the inguinal area. The clinical diagnosis of tumor of the spermatic cord is often very difficult to make. It has to be differentiated from such conditions as hernia, hydrocele of the cord, tuberculosis, syphilis, hematocele, and lymphatic enlargements. We therefore advocate surgical exploration on all questionable cases.

SUMMARY

Two cases of tumor of the spermatic cord have been presented with a brief review of the literature and the difficulties in diagnosis pointed out.

727 W. Seventh St., Los Angeles 14, Calif.

REFERENCES

EVANS, N. J. Urol., 50: 249-254, 1943
PRINCE, C. L. J. Urol., 47: 793-799, 1942
SHIVERS, C. H. J. Urol., 52: 266-274, 1944
STRONG, G. H. J. Urol., 48: 527-532, 1942
THOMPSON, G. J. Surg., Gynec. & Obst., 62: 712-728, 1936

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A CASE OF PREPENILE SCROTUM

L. F. HUFFMAN

On October 14, 1944 the writer was asked to see a week old infant in Elyria Memorial Hospital who was reported to show an interesting anomaly of the external genitalia and not to have urinated since birth. The referring physician had passed a soft rubber catheter and obtained a few drops of turbid fluid.

The patient was a robust infant of normal appearance except for the following described anomaly. A rather large scrotum containing both testicles was situated anteriorly in the pubic region. Posterior to this was a pendulous penis 7 cm. in length. The median raphe extended from the anus to the tip of the penis and was absent over the scrotum. The meatus and glans penis appeared normal. A soft rubber catheter, a metal catheter and infant cystoscope were passed through the urethra obtaining only a few drops of turbid fluid. Examination with the Beer infant cystoscope showed a small cavity lined with pale mucosa. It was impossible to locate any ureteral orifices or recognize any normal bladder landmarks. On rectal palpation only a very thin membrane intervened between the metal instrument in the bladder and the rectum. Examination of the rectum with the cystoscope yielded no additional information. The bladder cavity was distended to capacity with 10 cc of 15 per cent skiodan and an x-ray made (fig. 1). The following is the radiologist's report: "A film of abdomen shows no definite kidney shadow. The liver appears to be about normal size. A small catheter inserted in penis lies with its tip opposite the sacrum and after injection of contrast media there is a blind bag overlying the pelvis. It measures 2½ by 4 cm. on this film and probably represents a bladder. No contrast medium progresses beyond the outline of this blind bag. Therefore we cannot be certain that ureters enter this so-called bladder."

X-rays were made after injecting 5 cc skiodan subcutaneously but no visualization of the urinary tract was obtained.

Ten days later the infant was admitted to Fairview Park Hospital. Generalized edema was present (fig. 2). Although there was no visible excretion of urine the nurses noted that the bowel movements were more liquid than usual. The blood urea nitrogen was 78 mg. per cent, the creatinine 8.6. After indigo carmine injection it was thought that the bowel movements showed slight staining. Excretory urography again gave no information.

Exploration of the right kidney through the customary lumbar incision showed a kidney slightly larger than normal presenting the typical picture of congenital cystic kidney. The infant expired the following day, aged 19 days.

We anticipated obtaining further information at autopsy but this examination was refused. However, in view of the facts presented above we believe that we can assume that the patient, in addition to the anomaly of the external genitalia, had the ureters opening ectopically in the bowel.

DISCUSSION

A search of the literature has revealed only 2 similar cases. Francis reported a case of an "infant dying 47 minutes after delivery at term which showed most

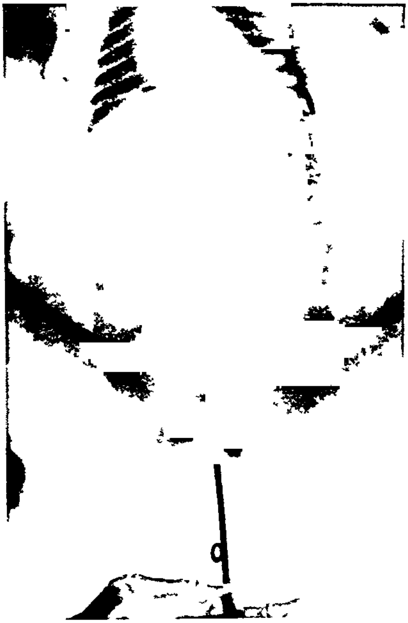
Fig 1

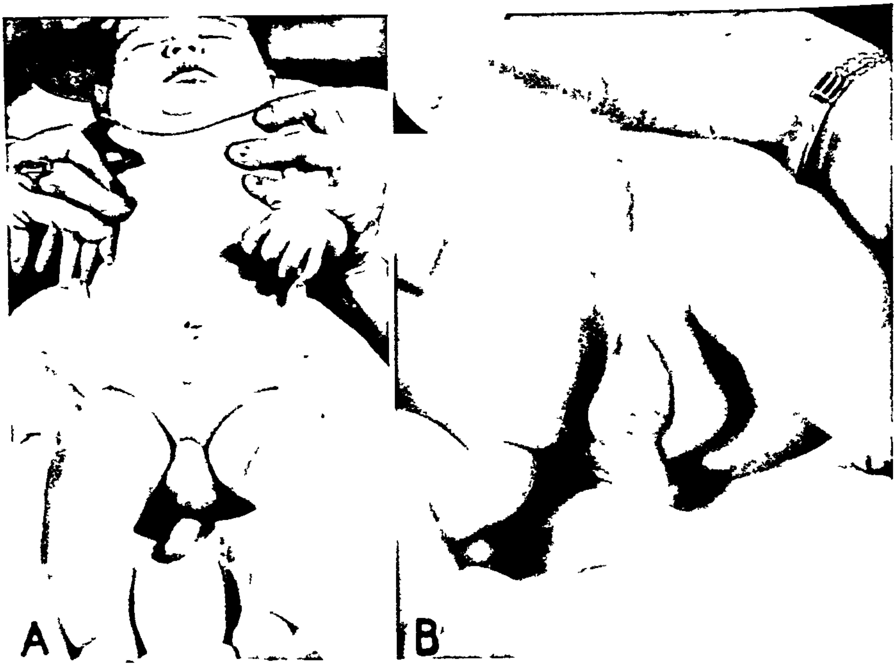

Fig 2

unusual malformations; complete absence of urinary system, prostate and right seminal vesicle—atresia and diverticulum of the pelvic colon—continuation of the abdominal aorta as a single umbilical artery and the following abnormality of the external genitalia. Externally the abnormal findings were confined to the perineum, buttocks and anal region. The scrotum was large, had no median raphe and was attached immediately above the symphysis. The perineum was undeveloped so that creases over the adductor muscles met in the midline. The penis placed about 3 cm. behind the scrotum, had a median ventral raphe and a rudimentary glans and prepuce. The navicular fossa was present in the glans but there was no penile urethra. The anus was dorsally placed and the tip of the coccyx projected backward, as in the chimpanzee. The buttocks were undeveloped and the greater trochanter on either side was easily palpable owing to the poor development of the gluteus maximum muscle. The position of the scrotum is difficult to explain but it would appear that in the absence of a urogenital sinus the scrotal swellings failed to shift caudad to the penis and therefore the scrotum developed anteriorly. This is the normal position in the Marsupialia."

In his search of the literature Francis found a case of Hildebrand quoted as follows: "Ivar Broman, on p. 506 of *Normale und Abnorme Entwicklung des Menschen*, presents an illustration of a child with perineal hypospadias and prepenial scrotum and states that the case was a patient of Prof. Hildebrand. No information is given but from the illustration the child was several months old, living and apparently healthy."

25 Prospect Ave. W., Cleveland 15, O.

REFERENCE

FRANCIS, C. C.: "Case of prepenial scrotum (marsupial type of genitalia) associated with absence of urinary system. Anat. Rec., 76: 303–308, 1940.

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SECONDARY TUMORS OF THE GENITO-URINARY TRACT

MILTON E. KLINGER

The literature has heretofore contained scattered and isolated references to cases in which the urinary tract has been involved by metastatic malignant growths. By and large these cases have had certain unusual and often bizarre characteristics which made them worthy of recording. With the exception of Willis' textbook on *The Spread of Tumors in the Human Body* no recent general review of the over-all picture of genito-urinary involvement by metastatic growths is to be found. Moreover, many are of the impression that metastatic invasion of the urinary tract is a unique and rarely encountered phenomenon. Such is, however, by no means the case, as the subsequent report will bear out.

The series of approximately 5000 autopsies performed at the Henry Ford Hospital to the year 1948 was reviewed and the cases of urinary involvement by metastatic malignant growths were selected to provide the basis for this account. Only those cases were included in which there was actual invasion of the urinary or genital structures, and in which a definite gap existed between the primary tumor and the metastatic deposit. Mere compression or spread by contiguity were not deemed metastatic in nature. The whole group of malignant neoplasms of the lower large bowel and the female generative tract which notoriously involve the urinary tract by compression and direct spread were eliminated unless a clear cut interval of normal tissue could be demonstrated indicating the existence of a true metastasis to one of the urinary organs in the female or the urogenital structures in the male.

One hundred and forty-two instances fulfilling the above criteria were found. The primary lesions were distributed as indicated in table 1.

Table 2 shows the distribution of the metastases to the urinary organs.

In the majority of instances (97) multiple portions of the urinary tract were affected. Many combinations were presented, the most common being bilateral renal involvement, next both kidneys and the bladder, then both kidneys and the prostate, and finally one kidney and the bladder. Table 3 details the combinations and their incidence.

In 45 of the cases a single portion of the urinary tract had been invaded. Table 4 shows the distribution in this type.

The distribution of the tumors which produced involvement of more than one portion of the urinary tract is outlined in table 5.

The tumors which showed spread to only a single portion of the urinary tract and their numerical distribution are indicated in table 6.

The following composite table gives a numerical indication of the incidence of involvement of each of the urogenital structures by the different primary tumors (table 7).

URINARY CHANGES

In the vast majority of cases abnormalities in the urine were more or less constantly present. Although these could in no way be considered specific or diagnostic, they do reflect the presence of pathologic change in the tissues of the urinary tract. Eighty-six cases showed such abnormalities, 48 did not, and in 8 no data were available. In the 48 cases without consistent deviations from normal such as pyuria, albuminuria, hematuria, or casts, the kidneys were involved in 43, the bladder in 6, the prostate in 2, the ureters in 1, and the seminal vesicles in 1. In 3 cases of renal involvement in the latter group there was extensive replacement of the parenchyma by the neoplastic tissue. All 3 were instances of leukemia and despite this widespread infiltration there were none of the abnormalities usually sought for in the routine analysis.

TABLE 1

Lymphomas (including acute and chronic leukemias, lymphosarcoma, Hodgkin's, and sarcoid)	47
Bronchus, lung, pleura	19
Stomach	16
Breast	12
Pancreas	8
Ovary	5
Esophagus	6
Biliary system	4
Kidney	3
Bone	4
Rectum	3
Cervix	2
Testicle	2
Tongue	2
Sigmoid	2
Ileum	1
Bladder	1
Uterus	1
Thyroid	1
Primary unclassified	3

TABLE 2

Bilateral renal involvement	85
Unilateral renal involvement	33
Bladder involvement	33
Prostatic involvement	10
Ureteral involvement	7
Testicular involvement	3
Seminal vesicle involvement	4
Vas deferens involvement	1
Urethral involvement	1
Penile involvement	1*

* In this patient a mass in the corpus cavernosum resulting in priapism led to a biopsy of the tissue which was described as "endothelioma" Subsequently the patient was found to have carcinoma of the left kidney It not infrequently occurs, according to Willis, that a metastatic tumor of the penis is mistaken for an endothelioma of the erectile tissue Such a situation may be represented here

Albuminuria. Fifty-three of the patients showed persistent albuminuria varying from 1 to 4 plus. In 41 of these one or both kidneys were involved, the ureters in 4 cases, the bladder in 16, the prostate in 6, the urethra in 1, the penis in 1, the testicles and seminal vesicles in 1. In the above group one or more of the structures named may have been affected concomitantly. In the 12 instances in which the kidneys were not affected by the growth, the bladder was involved alone in 6 instances, the bladder and urethra in 1, the right ureter alone in 1, the left ureter and bladder wall in 1, and the bladder, ureters and prostate in 1. The majority of cases were of the lymphoma group (22), and the next most frequent primary lesion in this group was carcinoma of the stomach (6).

TABLE 3

Both kidneys	68
Both kidneys and bladder	9
Both kidneys and prostate	4
One kidney and bladder	3
Both kidneys, bladder, seminal vesicles	1
Both kidneys, ureter, bladder	1
Both kidneys, both ureters	1
Both kidneys, prostate, seminal vesicles, testicle	1
Both kidneys, bladder, prostate	1
One kidney, both ureters, bladder	1
One kidney, prostate	1
One ureter, bladder	2
Both ureters, prostate, bladder	1
Bladder, prostate, testicle	1
Bladder, urethra	1
Testicle, vas, seminal vesicle	1

TABLE 4

Kidney alone	28
Bladder alone	13
Ureter alone	1
Prostate alone	1
Seminal vesicle alone	1
Penis alone	1

TABLE 6

Ca bronchus, lung, pleura	12
Ca stomach	8
Ca ovary	5
Ca breast	4
Ca rectosigmoid	4
Ca pancreas	2
Ca esophagus	2
Osteogenic sarcoma	2
Ca kidney	1
Ca ileum	1
Ca gallbladder	1
Ca breast	1
Ca cervix	1

TABLE 5

Lymphomas	46
Ca stomach	9
Ca lung, bronchus, pleura	7
Ca breast	7
Ca pancreas	6
Ca esophagus	3
Ca tongue	2
Ca testicle	2
Ca gallbladder	2
Fibrosarcoma	2
Ca cervix	1
Ca thyroid	1
Ca rectum	1
Ca colon	1
Ca uterus	1
Ca urinary bladder	1
Ca kidney	1
Melano-epithelioma	1
Malignant granuloma	1
Primary undetermined	2

Hematuria. Twenty-eight cases showed blood in the urine. This was rarely gross, but was persistent though microscopic. Twenty-two of these cases involved the kidneys, the involvement being unilateral in 4. Five of the remaining involved the bladder and 1 the penis. Three cases, 1 primary in the bladder with renal metastases, 1 primary in the kidney with metastases to the penis, and the final one primary in the kidney with metastases to the ureter and the bladder, would be likely in any event, to display hematuria.

This is a surprisingly small number of cases considering the fact that with few exceptions the urinary tract was involved in such a manner that egress to some portion of the collecting, storing, or discharging systems was available as indicated in the primary criteria for selection of the cases included in the study.

TABLE 7

TUMOR	BOTH KIDNEYS	ONE KIDNEY	BLADDER	PROSTATE	URETERS	TESTICLE	VESICLE	VAS	URETHRA
Lymphomas	45		9	4	1	1	3		
Breast	7	2	3						
Stomach	7	4	8		2	1	1	1	
Lung	6	11	2	1	1				
Pancreas	5	2	2	1					
Tongue	2								
Gallbladder	2	2							
Esophagus	2	2			1				
Thyroid	1								
Cervix	1	1	1						
Bladder	1								
Melanoma	1								
Granuloma	1			1					
Fibrosarcoma	1								
Osteosarcoma	1	2							
Ovary		3	2						
Ileum		1							
Rectosigmoid		2	3	1	1				
Testicle		1	1	2		1			
Kidney			1		1				
Uterus			1						1

The reason may be that actual ulceration of mucosa is not prone to occur in secondary lesions. This observation is moreover in agreement with the clinically recognized fact that many primary neoplasms of the urinary tract are not associated with persistent hematuria.

Of the primary lesions producing this sign, 7 were in the lymphoma group, 6 were in the gastro-intestinal tract, 3 in the breast, 4 in the female generative tract, 2 in the gallbladder, 1 in the pancreas, 3 in the urinary tract, 1 a fibrosarcoma, and 1 a malignant granuloma. An interesting feature with respect to hematuria in this series is that the incidence of cases in the lymphoma type of lesion was much less than in the case of metastatic lesions producing albuminuria.

Casts. The consistent presence of casts was noted in 49 cases. In 6 of these the metastatic lesion was elsewhere than in the kidney. Since casts originate in the

TABLE 8 *Metastatic site*

URINARY ABNORMALITY	KIDNEY	URETER	BLADDER	PROSTATE	SEM. VESICLE	TESTICLE
Albumin	Lymphoma 19 Stomach 6 Ovary 2 Rectosig 2 Fibrosarc. 2 Lung 4 Granuloma 1 Esophag 1 Gallbladder 1 Osteosarc. 1 Cervix 1 Testicle 1	Lymphoma 1 Stomach 2 Rectosig 1 Lung 1	Lymphoma 5 Stomach 4 Breast 2 Rectosig 2 Ovary 2 Cervix 1 Lung 1 Uterus 1	Lymphoma 3 Rectosig 1 Testicle 1 Granuloma 1	Lymphoma 1	Lymphoma 1
R B C	Lymphoma 6 Stomach 4 Gallbladder 2 Ileum 1 Pancreas 1 Rectosig 1 Ovary 1 Granuloma 1 Fibrosarc 1 Breast 1 Cervix 1	Stomach 1	Stomach 2 Breast 2 Cervix 1 Ovary 1 Uterus 1	Lymphoma 1 Granuloma. 1		
W B C	Lymphoma 16 Stomach 6 Pancreas 4 Breast 3 Ovary 3 Lung 2 Gallbladder 2 Esophagus 1 Rectosig 1 Testicle 1 Granuloma 1 Fibrosarc 2 Ileum 1 Cervix 1 Osteosarc 1	Lymphoma 1 Stomach 1 Lung 1	Lymphoma 5 Stomach 5 Breast 3 Ovary 2 Cervix 1 Testicle 1 Rectosig 1 Lung 1 Pancreas 1 Uterus 1	Lymphoma 2 Granuloma 2 Testicle 1		Testicle 1
Casts	Lymphoma 20 Stomach 4 Ovary 3 Pancreas 2 Lung 2 Gallbladder 2 Cervix 1 Testicle 1 Esophagus 1 Sarcoma 1 Granuloma 1 Breast 1 Ileum 1	Lymphoma 1 Rectosig 1 Stomach 1 Lung 1	Lymphoma 6 Rectosig 2 Stomach 1 Lung 1 Breast 1 Cervix 1 Uterus 1 Ovary 1	Lymphoma 3 Granuloma 1 Testicle 1 Rectosig 1	Lymphoma 2	Lymphoma 1

renal tubular system it must be assumed that the presence of casts resulted from some associated renal lesion, possibly toxic in nature secondary to the primary malignancy.

Pyuria. Fifty-nine cases showed pus cells in the urine. How much of this was due to associated bacterial infection and how much to the mere presence of the metastatic lesion was not always possible to say. In the majority, by far, there was not enough clinical evidence to ascribe the pyuria wholly to inflammatory causes. In some, such associated lesions as stone, inflammatory stricture, and so on were known to be independently present and could certainly have caused the pyuria, but in others it must be assumed that the presence of the metastatic lesion was at fault, possibly by exerting a foreign body irritant effect. Almost one third of the cases in this group were in the lymphoma series.

Table 8 shows the urinary changes in relation to the primary tumor and the urinary organ involved.

RENAL FUNCTION

One of the most interesting aspects of this study has been the observation of how renal function was affected by the invasion of metastatic growth. In 58 cases moderate to severe involvement of the kidneys was described in the autopsy protocol. The clinical records of these patients were carefully examined to determine what, if any, effect the destruction of renal tissue had. A blood nonprotein nitrogen of over 40 was taken as an index of gross impairment of renal function. Doubtlessly the more sensitive renal function tests would alter the figures relating to the number of cases with excretory deficiency. However, in few, if any, cases were such tests employed since in almost all instances attention was focused primarily on other organs, or the renal factor was not thought of sufficient importance to warrant intensive study. The latter fact is borne out by the observation that in the entire series there was scarcely a case in which the urinary tract metastases were specifically recorded as being present before death.

TABLE 9

Lymphoma group	10
Pancreas	2
Stomach	1
Bile ducts	1
Esophagus	1
Colon	1
Lung	1
Bladder	1
Cervix	1
Soft tissue of thigh	1

Of the 58 cases with moderate to extensive renal tissue replacement, there was evidence of renal insufficiency as judged by the above-noted criteria in 20 cases. Distribution of these cases as to primary lesion is indicated in table 9.

The degree of impairment varied from negligible nonprotein nitrogen elevations to instances in which patients succumbed to uremia. The latter merit more detailed analysis. Four were in the lymphoma series (1 aleukemic myelosis, 1 acute lymphatic leukemia, 2 lymphosarcoma); 1 was a carcinoma of the stomach with spread to the ureters as well as the kidneys so that there was the added factor of obstruction. This patient was anuric. One was a carcinoma of the bladder which also caused ureteral occlusion as well as extensive bilateral renal metastases, so that in this instance too the additional important factor of obstruction was present. The cases caused by the lymphomas usually involved renal destruction pure and simple. No obstructive factors were present.

In 9 cases deficient renal function was present despite the fact that there was no extensive destruction of renal tissue or in which metastases to the kidney were not conspicuous. In 4 of this group unrelated conditions (such as intestinal obstruction, vesical and renal calculi, stricture, and lower nephron syndrome) produced the elevation in nonprotein nitrogen. In 3 the elevation was insignificant, and in the remaining 2 both ureters were the seat of metastases (in 1 from the rectum and in the other from the pleura) with resulting bilateral hydronephrosis and hydro-ureter. Both the latter died in uremia further demonstrating the lethal effect of the obstructive factor.

In contrast to the above were the numerous instances in which there was a good deal of renal destruction but no evidence of renal failure. This was particularly striking in the lymphoma series where heavy and widespread infiltration were frequently noted without elevations in the blood urea nitrogen, bearing out the known clinical fact that a small amount of normally functioning renal tissue can sustain life, for a time, at least.

BLOOD PRESSURE

Any correlation of alterations in blood pressure with pronounced renal infiltration or destruction was inconstant and difficult to make out. There were 12 cases in the series with hypertension. In 6 of this group, extreme infiltration by leukemic, lymphosarcomatous, or granulomatous tissue of both kidneys was reported. The primary lesion in the others was in the breast, stomach, ovary, gallbladder, and ileum with considerable renal destruction and in some instances ureteral obstruction by tumor as well. In these cases there was no clear cut or convincing evidence of pathologic change in the kidneys other than the metastatic lesion which might account for the elevation in blood pressure. On the other hand, the blood pressure was normal in 15 cases of the lymphoma series and in 5 cases where the primary tumor was in the ovary, cervix, bone, pancreas, and pleura, all with renal damage equally as extensive as in the cases with hypertension. One patient with marked lymphosarcomatous invasion of both kidneys had a distinct hypotension.

While these observations would incline one to the belief that changes in blood pressure in the presence of renal metastases are very likely fortuitous, it cannot be denied that in some cases the renal damage occasioned by the metastases may be the basis for the hypertension.

URINARY SYMPTOMS

Of the entire series of 142 cases, 27 patients had clinical symptoms or signs related to the urinary organs. Oliguria or anuria was present in 4; 7 complained of painful urination; 4 had frequency; 5 had episodes of urinary retention; 1

was incontinent; and 2 complained of pain referable to one or another of the urinary organs. Critical evaluation of these symptoms in an attempt to determine whether or not the metastases were to blame or whether they were the result of incidental or concomitantly existing conditions disclosed the following:

Oliguria or anuria (4 cases). In 3 of these patients the urinary suppression was caused partly by extraneous factors. Of the latter, transfusion reactions were responsible in 2, and in 1 a possible mercurial nephrosis was to blame. The latter patient had a malignant endothelioma of the pleura with metastases to the right kidney, both ureters and the bladder. The ureteral metastases in this case produced bilateral hydronephrosis and hydro-ureter so that renal damage was already established before the onset of the mercurial reaction. Of the transfusion reactions one was in a patient with diffuse leukemic infiltration of the kidneys, bladder, and prostate; and the other was a case of carcinoma of the rectum with metastases to one kidney. The latter patient died of urinary suppression, the former did not. One may justifiably assume that pre-existing damage in the kidneys caused by infiltration or metastases makes recovery from the renal phase of reactions such as these less likely.

The final case of anuria was an instance in which the metastatic lesions were directly to blame having produced extensive renal destruction as well as obstruction in both ureters. The primary tumor in this case was a carcinoma of the stomach.

Painful urination (7 cases). One would expect to encounter involvement of the lower urinary tract if the neoplastic disease were to be the cause of this symptom. Of the 7 cases in this group only 3 had invasion of the urinary bladder, and in one of these the presence of associated prostatitis could have been the basis for the patient's symptoms. All 3 of these cases had carcinoma of the stomach as the primary lesion. In all 3 the tumor had metastasized to the bladder wall. In the remaining patients with the symptom of painful urination such other conditions as cystitis, urethrotrigonitis, hydronephrosis and calculus were present, but no actual invasion of the bladder or urethra by the tumor. There were, on the other hand, numerous instances in which the bladder was involved without the production of this symptom.

Urinary retention (5 cases). In only 2 of these 5 patients were the metastases directly responsible for the retention. In 1 patient it resulted from bladder and prostatic involvement by carcinoma of the testicle. In the other, spinal cord metastases from carcinoma of the bronchus resulted in bladder paralysis. The remaining 3 cases showed no cause of a malignant nature in the lower urinary tract. Two were carcinoma of the stomach and 1 an aleukemic myelosis with bilateral renal invasion only. The precise cause of the urinary retention in these 3 cases remains unexplained. It may be, though the records were not clear on this point, that because of inadvertent lack of attention to the bladder in these patients, that structure may have been permitted to become hypotonic to the point of complete retention.

Frequency of urination (4 cases). The bladder was affected in 2 cases, in 1 by spread from carcinoma of the breast and in the other by carcinoma from the ovary. In the other 2 cases, however, the bladder was not involved. A stomach carcinoma involved the right ureter causing hydronephrosis and hydro-ureter in 1, and in the other both kidneys presented metastases from a sigmoid lesion.

Nocturia (4 cases). In 3 of these 4 cases this symptom could be explained directly by the metastatic disease for involvement of the prostate was a notable feature. In one the prostate was found to have metastases from a carcinoma of the lung though this was not evident in life and not suspected in spite of the symptoms. In the second a chronic malignant granuloma involving the prostate by metastases produced induration and enlargement of the gland. This had been noted during life but the clinical diagnosis of "chronic nephritis" was thought to explain the symptom. Sufficient obstruction to warrant surgical intervention was not present else the diagnosis might have been established before death. In the third case there was prostatic involvement by a lymphosarcoma. This patient had hesitancy as well as nocturia, and died in uremia from extensive bilateral renal destruction caused by the primary disease. In the final case only the right kidney was involved in spread from a carcinoma of the ovary but no invasion of the lower urinary tract was present.

Pain (2 cases). The kidneys were involved in both these cases. In 1 however, a carcinoma of the kidney with metastases to the ureter and bladder, there were associated calculi which could have caused the symptom if indeed the primary disease did not. In the other patient there was bilateral tenderness over the kidney regions resulting from extensive destruction of both kidneys by carcinoma from the pancreas. In this case the possibility of renal neoplasm was suspected during life although its metastatic nature was not specifically noted.

In contradistinction to this relatively small number of cases which presented urinary symptoms, there was a large number which could have been expected to do so by virtue of the nature of the invasion of the urinary structures and yet did not. For example: There were 88 cases of renal involvement, 22 of bladder, 6 of prostatic, 2 of urethral, 3 of seminal vesicle, 1 of testicular, and 1 of urethral invasion in which the patients did not complain of any urinary symptoms which might have led one to suspect spread to these structures from the primary lesion.

UNUSUAL CASES

A group of cases is included in this series which merits recording purely because of the uniqueness of the cases in presenting infrequently encountered metastatic involvement of one or another portion of the urinary or genital tracts. They follow:

1) Carcinoma of the stomach with metastases to the right testicle, vas deferens, and seminal vesicle.
2) Carcinoma of the stomach with metastases to the right ureter.
3) Carcinoma of the pancreas with metastases to the prostate.
4) Carcinoma of the esophagus with metastases to both ureters.
5) Carcinoma of the tongue with metastases to both kidneys.
6) Bronchogenic carcinoma with metastases to the bladder.
7) Carcinoma of the lung with metastases to the prostate.

8) Periosteal sarcoma of the femur with metastases to the kidney.

9) Malignant endothelioma of the pleura with metastases to both ureters, bladder, and right kidney.

10) Fibrosarcoma of the mastoid with metastases to both kidneys.

11) Osteogenic sarcoma of the sternum with metastases to the right kidney.

12) Carcinoma of the kidney with metastases to the penis.

13) Teratoma of the testicle with metastases of the contralateral testicle, prostate, and bladder.

14) Chronic malignant granuloma with metastases to the prostate.

15) Hodgkin's disease with nodules in the ureteral wall and in the wall of the bladder.

16) Lymphosarcoma with metastases to the seminal vesicles, bladder, and kidneys.

17) Lymphosarcoma with metastases to the prostate, seminal vesicles, testicle and kidneys.

18) Lymphosarcoma with metastases to the seminal vesicles.

SUMMARY AND CONCLUSIONS

One hundred forty-two cases of secondary tumors of the urinary tract in the female and the urogenital tract in the male are reviewed.

The kidneys are the most frequent site of involvement, and the bladder next.

The most common lesions involving the urinary organs by metastases are those in the lymphoma group. Exclusive of these, the kidneys are most often involved by spread from carcinoma of the lung, and the bladder by spread from carcinoma of the stomach.

Of the genital structures in the male the prostate is most commonly involved. The predominant lesion is again the lymphomatous disease group.

Sixty per cent of the patients in this series showed urinary abnormalities. These were not invariably indicative of metastases, but their presence in a patient with malignant disease should at least lead one to suspect urinary involvement.

As a rule renal insufficiency is not an important feature unless the renal destruction is extreme, unless it is combined with ureteral obstruction, or unless the already damaged kidney becomes the seat of a superimposed disorder.

Blood pressure response to renal involvement is a variable thing, it being normal in as many cases with pronounced involvement as it was elevated.

Clinical symptoms or signs related to the metastases occur in approximately 20 per cent of patients.

Eighteen cases of unique metastases are recorded for their historical interest.

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REFERENCE

WILLIS, R. A.: The Spread of Tumors in the Human Body. London: J. A. Churchill Co., 1934.

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ALLERGY AND DRUG HYPERSENSITIVITY OF THE URINARY TRACT

J. S. EISENSTAEDT

The sparsity or almost complete absence of articles in the English language on the subject under consideration is very striking. Drs. Kendall and Nichols,[1] in their article appearing in the *Journal of Urology* less than one year ago, cite no references to American or British urologists on allergy of the urinary tract but do refer to two American publications on the general subject of allergy; viz., one by A. H. Rowe[2] and the second by Urbach and Gottlieb.[3] The second edition of S. M. Feinberg's[4] *Allergy in Practice* contains significant material on these manifestations of allergy. Some of the following references are from their outstanding books. The European literature is fortunately richer in contributions on this subject and has been reviewed in preparation for this paper.

It has been definitely proven that allergens and certain drugs may produce very marked symptoms and physical findings in certain individuals and that the changes produced may occasionally involve the urinary tract.

Obviously a urologist ordinarily is not trained as an allergist and vice versa, therefore the definitive diagnosis of these conditions may have to rest with the allergist. However, when the urologist has exhausted every means of diagnosis at his disposal and then by exclusion thinks that the patient may have an underlying causal allergic condition, he may refer the patient to the allergist and await his diagnosis, if the allergist can make one.

Allergy is to be considered as a condition appearing after previous sensitization (even in utero) based on an antigen-antibody reaction and manifested as a hypersensitiveness to a primarily nontoxic antigen. There is no fundamental difference between the allergic and the so-called nonallergic individual. The response of the allergic person differs from that of the so-called nonallergic in degree or distribution, not in kind. Allergy is primarily a protective reaction in which the normal physiology has been disturbed. It represents a response to an environmental maladjustment. It is a purposeful reaction, aimlessly executed, a perversion of the function of protecting the body against deleterious substances and environmental influences. It is usually a reversible reaction representing disturbed physiology rather than an organic pathological change. There is undoubtdedly a greater family incidence in the frankly allergic. It is possible that the vago autonomic system may play an important integrating part in constitutional allergic response. Unquestionably, in many instances of allergic reaction, there is likewise a psychogenic factor involved. I shall not pursue these phases further for obvious reasons.

Read at meeting of the Chicago Urological Society, January 26, 1950.

[1] Kendall, L. and Nichols, T. T.: J. Urol., 61: 222, 1949.

[2] Rowe, A. H.: Food Allergy. Philadelphia: Lea and Febiger, 1931.

[3] Urbach, E. and Gottlieb, P. M.: Allergy. Philadelphia: Grune and Stratton, p. 849, 1947, 2nd ed.

[4] Feinberg, S. M.: Allergy in Practice. Chicago: Year Book Publishers, 2nd edition, 1946.

The intensity of the reaction appears to be entirely out of proportion to the strength of the stimulus.

HISTORY

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Clinical observations and animal experiments of the last few years have disclosed that under certain conditions, all parts of the urinary tract may present symptoms of hypersensitiveness. We know this to be true of the kidneys, ureters, bladder and urethra. It must be borne in mind that the symptoms of urinary tract allergy are much like those of the common or usual urologic diseases. Since allergic conditions involving this system are relatively uncommon, it is incumbent on the physician to establish the diagnosis most carefully. Important in this relation are 1) family and personal history, as above outlined, 2) searching physical examination, making use of all modern urological diagnostic techniques, combined with very careful and painstaking laboratory procedures, and clinicopathologic tests.

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Any or all portions of the urinary tract may manifest symptoms of allergy, from the kidney to the external urinary meatus. Instances of renal allergy are numerous. Renal colic on an allergic basis has been described by Rowe,[2] Duke,[5] Miller and Uhle,[6] and also when it is accompanied by albuminuria and hematuria, as described by Rhodes[7] and Miller and Uhle. Renal symptoms sometimes appear as a part of a generalized allergic state; for example, Adelsberger[8] described the onset of hematuria following an injection of house dust extract in an asthmatic patient. It would take too long to detail the many cases of renal allergy reported; however, the following conditions are described:

Hematuria of 15 months' duration due to food and inhalation allergy, and 1 case of acute hematuria associated with allergic purpura, precipitated by the inhalation of tar fumes, the patient having previously been sensitized by chewing tar as a child. Renal and ureteral colic has been reported by several authors, subsequent to the ingestion or imbibition of several articles of food and drink.

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[5] Duke, W. W.: N. Y. State M. J., 116: 505, 1922; also Ann. Int. Med., 1: 117, 1922.
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[7] Rhodes, J.: J. Urol., 38: 410, 1937.
[8] Adelsberger, L.: Deut. med. Wochenshrft, 57: 585, 1931.

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ALLERGY AND DRUG HYPERSENSITIVITY OF THE URINARY TRACT

J. S. EISENSTAEDT

The sparsity or almost complete absence of articles in the English language on the subject under consideration is very striking. Drs. Kendall and Nichols,[1] in their article appearing in the *Journal of Urology* less than one year ago, cite no references to American or British urologists on allergy of the urinary tract but do refer to two American publications on the general subject of allergy; viz., one by A. H. Rowe[2] and the second by Urbach and Gottlieb.[3] The second edition of S. M. Feinberg's[4] *Allergy in Practice* contains significant material on these manifestations of allergy. Some of the following references are from their outstanding books. The European literature is fortunately richer in contributions on this subject and has been reviewed in preparation for this paper.

It has been definitely proven that allergens and certain drugs may produce very marked symptoms and physical findings in certain individuals and that the changes produced may occasionally involve the urinary tract.

Obviously a urologist ordinarily is not trained as an allergist and vice versa, therefore the definitive diagnosis of these conditions may have to rest with the allergist. However, when the urologist has exhausted every means of diagnosis at his disposal and then by exclusion thinks that the patient may have an underlying causal allergic condition, he may refer the patient to the allergist and await his diagnosis, if the allergist can make one.

Allergy is to be considered as a condition appearing after previous sensitization (even in utero) based on an antigen-antibody reaction and manifested as a hypersensitiveness to a primarily nontoxic antigen. There is no fundamental difference between the allergic and the so-called nonallergic individual. The response of the allergic person differs from that of the so-called nonallergic in degree or distribution, not in kind. Allergy is primarily a protective reaction in which the normal physiology has been disturbed. It represents a response to an environmental maladjustment. It is a purposeful reaction, aimlessly executed, a perversion of the function of protecting the body against deleterious substances and environmental influences. It is usually a reversible reaction representing disturbed physiology rather than an organic pathological change. There is undoubtedly a greater family[4] incidence in the frankly allergic. It is possible that the vago autonomic system may play an important integrating part in constitutional allergic response. Unquestionably, in many instances of allergic reaction, there is likewise a psychogenic factor involved. I shall not pursue these phases further for obvious reasons.

Read at meeting of the Chicago Urological Society, January 26, 1950.

[1] Kendall, L. and Nichols, T. T.: J. Urol., 61: 222, 1949.

[2] Rowe, A. H.: Food Allergy. Philadelphia: Lea and Febiger, 1931.

[3] Urbach, E. and Gottlieb, P. M.: Allergy. Philadelphia: Grune and Stratton, p. 849, 1947, 2nd ed.

[4] Feinberg, S. M.: Allergy in Practice. Chicago: Year Book Publishers, 2nd edition, 1946.

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[7] Rhodes, J.: J. Urol., 38: 410, 1937.

[8] Adelsberger, L.: Deut. med. Wochenshrft, 57: 585, 1931.

Instances of renal or ureteral colic precipitated by drinking beer has been reported by Urbach, by drinking milk, by Litzner.[9] Gutmann[10] has reported cases due to the ingestion of meat and fruit, and Adelsberger and Munster,[11] a case following ingestion of rhubarb. When the suspected incriminated substances were removed from the diet, the cramping pains disappeared, and only recurred after renewed exposure to the suspected substance. This, I believe, provides an allowable suspicion of allergy as a basis for the colic and cramping pains noted by their patients.

At this point it may be pertinent to state that strong support for an allergic basis is approved, when an attack of renal or ureteral colic fails to be relieved by the usual spasm-relieving drugs, and is relieved promptly by an injection of epinephrin, though the relief from this drug may only be temporary.

There has been a great amount of excellent research and carefully noted observations on the subject of glomerulonephritis from the point of view of allergy, and many think that glomerulonephritis is an allergic response to proteins of bacterial origin. This condition as well as the response of the kidney is serum sickness and in peri-arteritis nodosa usually fall in the realm of the internist and will not be discussed in this paper, though they are of great significance as a part of the general subject.

Duke has reported cases of painful urination or constant pain in the bladder area, without any objective findings, and suggests that the possibility of allergy should be considered, and the symptoms may appear as a part of a generalized allergic condition or as an isolated manifestation due to hypersensitiveness usually to some ingested allergen. Salen[12] reports a case of severe urinary urgency due to eating Brazil nuts and noted numerous eosoinphils in a sterile bladder urine. The eosinophils disappeared from the urine after the patient received anti-allergic treatment. Rowe describes strong contractions of the bladder associated with involuntary micturition, following the therapeutic injection of extract of mule dander. Litzner described forceful bladder contractions and dysuria following ingestion of flour and milk. The urine of this patient also contained numerous eosinophils and was sterile.

The absorption of unaltered allergenic proteins from the bladder in monkeys and humans has been demonstrated by Baretz, Harten and Walzer.[13] The urethra may react allergically. We all have seen cases from rubber contraceptive devices, producing balanitis and urethritis. Recently I have observed a case in which the most inexpensive contraceptive sheath did not cause any reaction while two more expensive brands produced significant and painful irritation. Skin tests were positive.

Hemoglobinuria and cold urticaria are also reported due to hypersensitivity to the bean Vicia-fava, known as favism, associated with systemic reactions. It is also thought that hemoglobinuria due to Plasmodium falciparum represents an allergic reaction, in that intracutaneous injections of killed plasmodia elicited positive reactions, namely hemoglobinuria, only in individuals who had had the disease.

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[9] Litzner, S.: Med. Klinic, 32: 630, 1936.
[10] Gutmann, M. J.: Med. Welt., 4: 739, 1930.
[11] Adelsberger, L. and Munter H.: Med. Klinic, 27: 294, 1926.
[12] Salen, E. B.: Acta med. Scand., 78: 197, 1932.
[13] Baretz, L. H., Harten, M. and Walzer, M.: J. Urol. 50: 71, 1943.

Bray[14] states that enuresis may be associated with allergy, more particularly food allergy. It may be the only manifestation or may accompany other symptoms of allergy. In an allergic study of 15 children with enuresis, three were relieved following the avoidance of positive foods.

Recently a number of reports of allergy due to the sulfonamides affecting the kidney have been reported and this phenomenon has been well described.

Various allergic manifestations occurring just before or during the menstrual period and cases of vaginitis associated with hay fever caused by ragweed as reported by Feinberg are well known and will not be described here.

The symptoms due to the allergic disease are identical with similar symptoms due to the pathologic processes causing them in the usual urologic diseases. Those which have come under my observation are frequency and dysuria, hematuria, renal colic and urethritis, and only by elimination of all the usual etiologic factors by every known method of diagnosis should one be led to the suspicion of an allergic basis in any given case. Kendall and Nichols state the symptoms of dysuria and frequency are due to an allergic edema of the mucous membrane of the ureter or urethra. They also agree that psychic factors are an important consideration in the predisposing, precipitation and maintenance of allergic diseases.

OBJECTIVE FINDINGS

Hematuria may be of any degree from the finding of a few red blood cells in the urine to a frank red or portwine urine. Bacteria are not found in early cases. Few leukocytes are seen, and these when stained by Wright's stain are recognized usually as mononuclear leukocytes and frequently are eosinophilic. In some instances all leukocytes may be eosinophilic. In chronic cases, according to Kendall and Nichols, bacteria and polymorphonuclear leukocytes as well as mononuclears and eosinophils are found.

It must be again emphasized that no part of a complete urologic study including guinea pig inoculation may be omitted and that only if all of the findings compatible with the common causes of symptoms noted by these patients are absent, may one then consider the possibility of an allergic basis. This cannot be overstressed, and I would deeply regret having any urologist, on flimsy suspicions of an allergic origin, dismiss a patient without the most complete and painstaking study.

CASE REPORTS

I have observed 5 cases which I believe to have had urinary symptoms of lesser or greater degree due to allergy or drug idiosyncrasy. I shall briefly outline them. In all instances a competent allergist has carried out the necessary tests and in all 5, the specific allergin or drug was determined. In 2 other cases not included in this group, the patients showed hypersensitivity to so many substances that it was impossible to unravel the problem. In 1 instance, a Negro, the patient reacted positively to over 100 substances and in the other, a white woman, reacted to over 60 substances. In the latter patient though only a rare red blood cell was seen and an occasional leukocyte was found in the urinary sediment these were eosinophilic mononuclear leukocytes.

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[14] Bray, G. N.: Arch. Dis. Childhood, 6: 251, 1931; also Recent Advances in Allergy, Philadelphia: P. Blakiston Sons and Co., 1934, 2nd ed.

Case 1. The first case observed was seen in 1939. The patient was a white man aged 49, who voided red urine, loaded with blood cells. He had been very carefully studied elsewhere and all findings except the presence of red blood cells were negative. There was no associated pain nor colic. All tests and examinations were meticulously repeated on several occasions here and were found negative. This being my first case, I was rather inept in asking all the important questions in the history; and there is no significant comment about other allergic manifestations. However, completely at the end of my resources in an attempt to determine the etiology of the bleeding, I referred the patient to an allergist. He was found to be allergic to several substances, but reacted much more strongly to milk than to the others. The patient's occupation was that of inspector of dried milk plants and after eliminating all milk from his diet, though he showed marked improvement, his urine still contained many red blood cells until an inhalator was purchased for him to wear while inspecting these plants. Naturally, he was required to wear white cotton suits and cap which he discarded when leaving the plants. All red blood cells disappeared from his urine for as long a period as he carefully abstained from all types of contact with milk or milk products. The patient can produce hematuria at will when exposed to milk in any form, including the fine dust at the dried milk plants.

Case 2. The wife of a physician had had several attacks of renal colic associated with the presence of red blood cells in the urine. Again all examinations were negative except for positive culture of B. alkaligenes. She gave a history of pyelitis in childhood and its recurrence during pregnancy. After repetition of all types of genito-urinary examinations with completely negative findings except for the presence of bacteria, she was sent to an allergist for study. It was found that she also was allergic to several allergens. However, before the study was completed she had another attack of colic associated with red blood cells which followed the taking of codeine phosphate for a toothache. We did not consider this significant until after an interval of 4 months, codeine was again prescribed in a cough mixture, followed again by severe renal colic. This patient remains free of colic, which can be produced by the taking of codeine. Thus I bel eve this case can be classed as one of drug allergy rather than of drug idiosyncrasy.

Case 3 is almost identical with case 2; the patient also is the wife of a physician. She had complained of recurrent kidney colic with the presence of red blood cells in the urine. She had been studied at a prominent clinic in the Northwest and all physical and laboratory tests were found to be negative. All modes of examination were repeated here, all with negative results. She was referred to an allergist and while undergoing a rather lengthy series of tests she, for the first time in her life, developed a very severe attack of bronchial asthma, after the ingestion of a salad with Roquefort cheese dressing. She required repeated injects of neosynephrin during the night. She was found to be sensitive to molds and since studiously avoiding this group of allergens she has remained well and has been free from urinary symptoms.

Cases 4 and 5. For the sake of brevity cases 4 and 5 may be described together because they paralleled each other almost perfectly. They represent drug idiosyncrasy rather than drug allergy. In drug idiosyncrasy one observes the manifestation to an unusual degree of a normal pharmacologic reaction or side reaction, while in drug allergy the response is entirely abnormal, such as for example as is seen in cases of sulfonamide allergy. In this condition the symptoms manifested are entirely independent of the physiologic action of the drug, and are characteristic of atopy, namely a hereditary factor in hypersensitivity.

To refer back to cases 4 and 5 they concerned elderly men, one of whom was known to be markedly allergic to various proteins and for which the medication was given and the other less minutely observed suffered from asthma—again receiving the medication for his condition. The substance given in both instances was ephedrin in physiologic doses. Both men had enlarged prostates, but had little or no difficulty in voiding. Both men were in complete retention within 36 hours after taking ephedrin. Strangely enough, both patients had received the drug on prescription by the same physician. After the elimination of ephedrin from their treatment both men resumed their usual urinary status and required no further treatment. It is well to remember that after taking ephedrin in physiological doses, that the tone of the muscle of the trigone and vesical sphincter is definitely increased and that retention of some degree is very prone to occur in men of prostatic age. Other patients receiving full therapeutic doses may complain of difficulty and discomfort in voiding as described by Boston,[15] Balyeat and Rinkel,[16] and Valentine and Fitzgerald.[17]

DISCUSSION

The fact that infrequently or rarely any or all organs of the urinary tract may be the site of an allergic response has been stated. That these manifestations may be part of a systemic allergic response or represent an isolated locale has been noted. The symptoms occurring as a result of allergy in the urinary tract are identical with those due to the more usual causes. The physician must make use of every possible method of examination, inclusive of laboratory methods to exclude organic disease. The history may be of great significance in helping one come to a presumptive diagnosis of allergy. The eventual diagnosis will probably always lie with the trained allergist.

The characteristic finding of preponderance of mononuclear leukocytes in the urinary sediment, many or all of which are eosinophiles, suggests the likelihood of an allergic basis. The failure of response of urinary colic to the usually prescribed antispasmodic drugs and its rapid, though temporary response to neosynephrin may also suggest an allergic origin of the cramping pains.

Elimination of the offending substance with complete freedom from symptoms is very significant, especially if, after an interval, exposure to the allergen reproduces the symptom complex for which the patient sought relief.

25 E. Washington St., Chicago, Ill.

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[15] Boston, L. N.: Med. Times, 56: 94, 1928.
[16] Balyeat, R. M. and Rinkel, H. J.: J. A. M. A., 98: 154, 1932.
[17] Valentine, J. J. and Fitzgerald, J. S.: J. Urol., 34: 314, 1935.

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A NEW FENESTRATED TROCAR FOR INTRODUCTION OF BALLOON CATHETERS IN CYSTOSTOMY, NEPHROSTOMY AND PYELOSTOMY

MEREDITH CAMPBELL

From the Department of Urology, New York University-Bellevue Medical Center, N. Y.

Except for McIver's ingenious solution of the problem of size and bulk of the outer end of the Foley catheter with its two tubes (one for drainage and one for balloon inflation), the universally employed balloon catheters cannot be completely passed through cystostomy trocars heretofore available. The instrument described here was designed to overcome this difficulty and does so.

Since the introduction of the balloon catheter by Foley, these self-retaining instruments have largely superseded the mushroom (de Pezzer) and wing-tipped (Malecot) tubes so regularly employed previously. No attempt has been made by me to introduce mushroom catheters through the new instrument (fig. 1) here described since I long ago discarded them because withdrawal of the large mushroom head is needlessly traumatic. Yet by using a probe or stylet to stretch the tip of the winged catheter and thus flatten out the wings, this catheter is easily passed through the fenestrated trocar to the bladder or renal pelvis (fig. 2, *A*). Small balloon catheters (14 to 18F) of the Foley type or the Higgins' modification pass readily without a stiffening stylet or probe but the balloon segment of a 20F catheter might be a tight fit and requires the assistance of a stylet.

When this instrument was initially conceived the first one for experimental trial was fashioned from a Young urethroscope, at the inner third of which was made a fenestra of less than half the diameter of the tube and about 5 cm. long. The solid stylet was spear pointed. This trocar was used for cystostomy in several patients and served admirably. The present instrument* is shown in fig. 1 where it will be noted that for guidance the stainless steel 26F tube is appropriately calibrated in centimeters, registering from the tip of the hollow ground three sided sharp edged stainless steel solid obturator. A wide, round, thin flange at the outer end of the tube materially assists manipulation of the trocar.

To use the trocar for cystostomy under local anesthesia, the bladder is well filled to elevate the peritoneal reflection reasonably high above the pubis. The skin and projected path through which the trocar will be passed into the bladder is infiltrated with 1 per cent novocain. Introduction of the instrument is facilitated by making a small skin incision 1 cm. long. In a child the trocar is introcuced about 2 cm. above the upper border of the pubis and in an adult about 4 cm., the direction being downward and slightly forward toward the juxtatrigonal bladder floor. The instrument is now pushed directly through the abdominal wall and into the bladder; its arrival in this viscus is announced by slight leakage of bladder fluid and/or urine through the fenestra (fig. 2,*A*). The

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* Made by C. R. Bard, Inc., Summit, N. J.

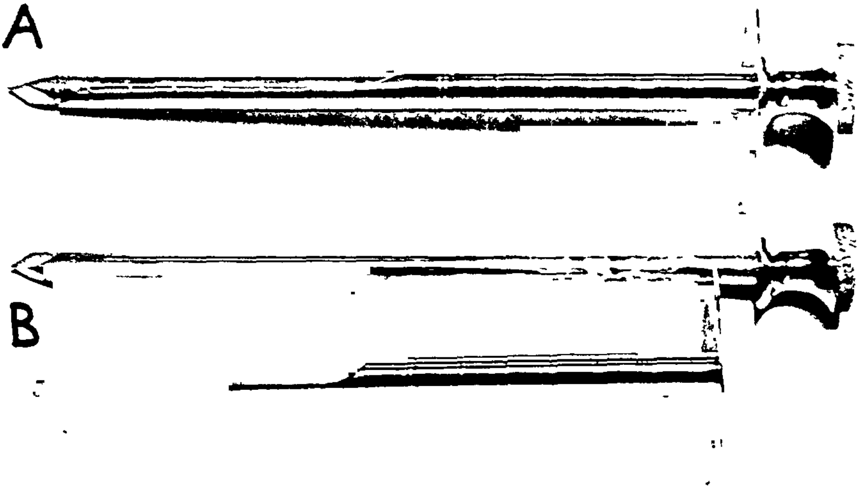

FIG. 1. Trocar opened and closed. Drainage tube is introduced through lateral fenestra

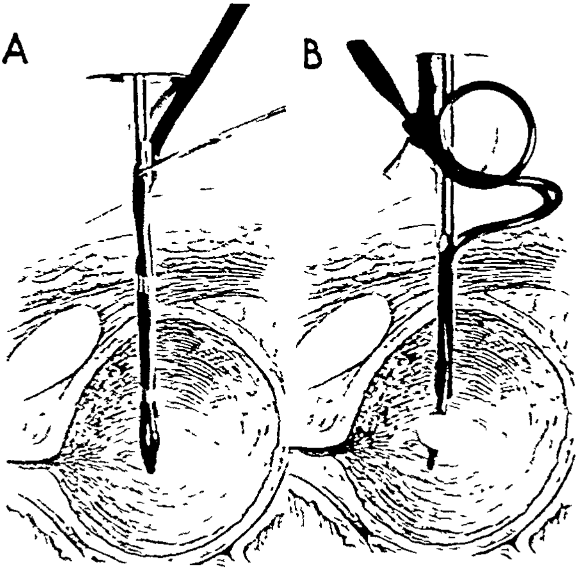

FIG. 2 *A*, trocar cystostomy with introduction of a wing-tip catheter elongated with a probe. *B*, trocar cystostomy with introduction of balloon catheter.

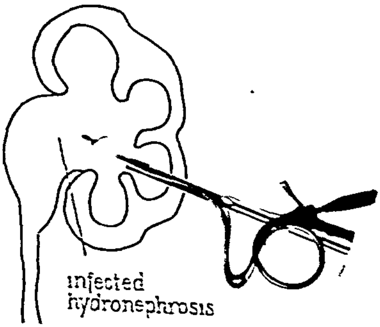

FIG. 3. Trocar nephrostomy with establishment of balloon catheter drainage

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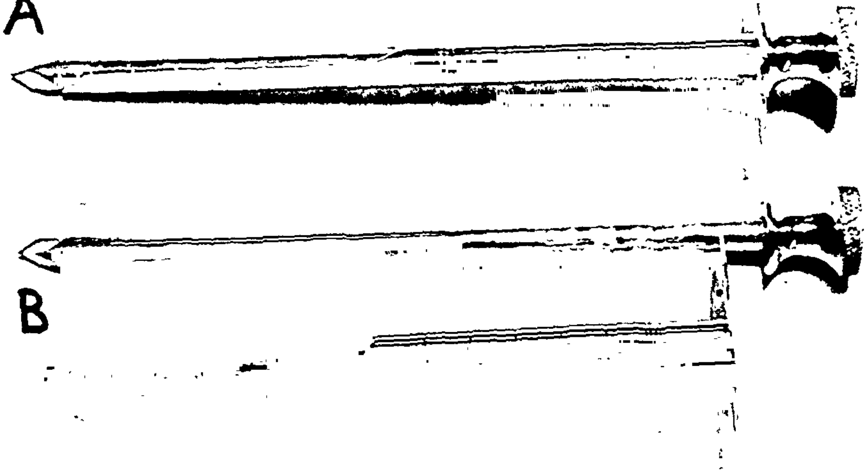

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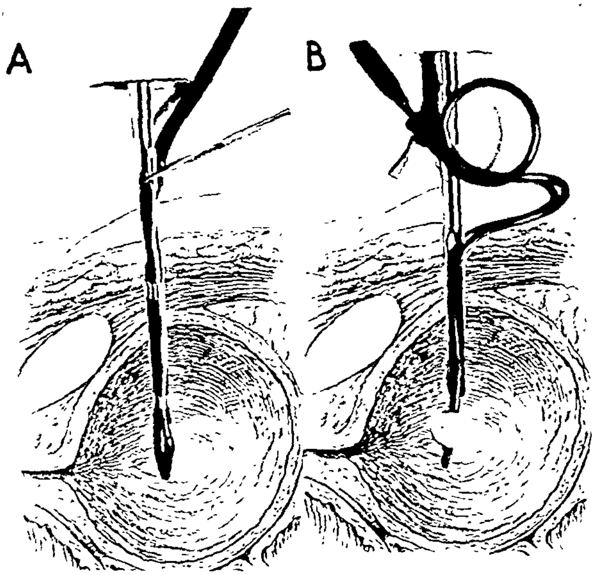

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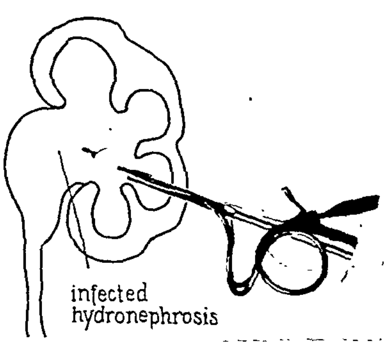

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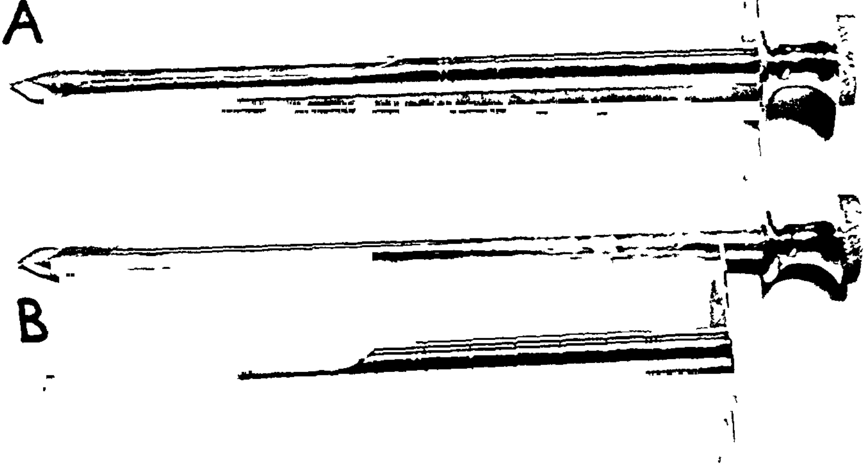

FIG. 1 Trocar opened and closed. Drainage tube is introduced through lateral fenestra

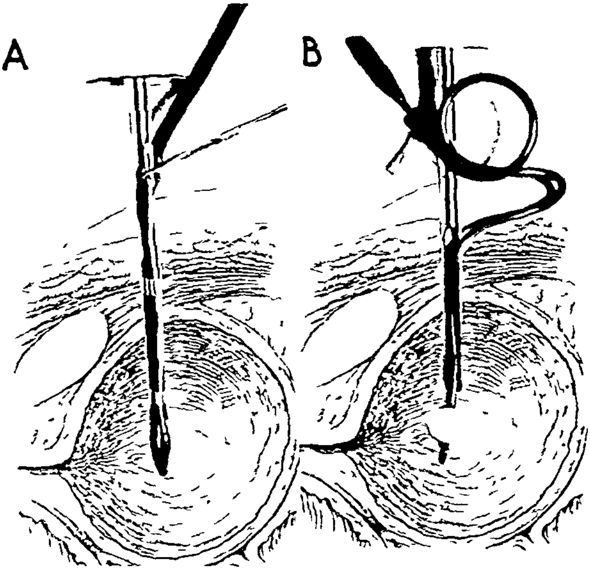

FIG 2 *A*, trocar cystostomy with introduction of a wing-tip catheter elongated with a probe *B*, trocar cystostomy with introduction of balloon catheter.

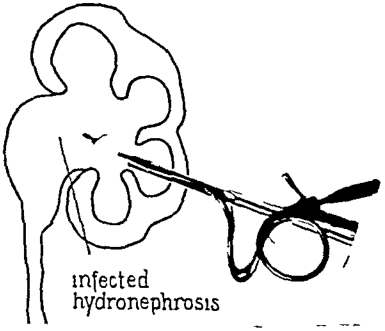

FIG 3 Trocar nephrostomy with establishment of balloon catheter drainage

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A NEW FENESTRATED TROCAR FOR INTRODUCTION OF BALLOON CATHETERS IN CYSTOSTOMY, NEPHROSTOMY AND PYELOSTOMY

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Except for McIver's ingenious solution of the problem of size and bulk of the outer end of the Foley catheter with its two tubes (one for drainage and one for balloon inflation), the universally employed balloon catheters cannot be completely passed through cystostomy trocars heretofore available. The instrument described here was designed to overcome this difficulty and does so.

Since the introduction of the balloon catheter by Foley, these self-retaining instruments have largely superseded the mushroom (de Pezzer) and wing-tipped (Malecot) tubes so regularly employed previously. No attempt has been made by me to introduce mushroom catheters through the new instrument (fig. 1) here described since I long ago discarded them because withdrawal of the large mushroom head is needlessly traumatic. Yet by using a probe or stylet to stretch the tip of the winged catheter and thus flatten out the wings, this catheter is easily passed through the fenestrated trocar to the bladder or renal pelvis (fig. 2, *A*). Small balloon catheters (14 to 18F) of the Foley type or the Higgins' modification pass readily without a stiffening stylet or probe but the balloon segment of a 20F catheter might be a tight fit and requires the assistance of a stylet.

When this instrument was initially conceived the first one for experimental trial was fashioned from a Young urethroscope, at the inner third of which was made a fenestra of less than half the diameter of the tube and about 5 cm. long. The solid stylet was spear pointed. This trocar was used for cystostomy in several patients and served admirably. The present instrument* is shown in fig. 1 where it will be noted that for guidance the stainless steel 26F tube is appropriately calibrated in centimeters, registering from the tip of the hollow ground three sided sharp edged stainless steel solid obturator. A wide, round, thin flange at the outer end of the tube materially assists manipulation of the trocar.

To use the trocar for cystostomy under local anesthesia, the bladder is well filled to elevate the peritoneal reflection reasonably high above the pubis. The skin and projected path through which the trocar will be passed into the bladder is infiltrated with 1 per cent novocain. Introduction of the instrument is facilitated by making a small skin incision 1 cm. long. In a child the trocar is introcuced about 2 cm. above the upper border of the pubis and in an adult about 4 cm., the direction being downward and slightly forward toward the juxtatrigonal bladder floor. The instrument is now pushed directly through the abdominal wall and into the bladder; its arrival in this viscus is announced by slight leakage of bladder fluid and/or urine through the fenestra (fig. 2,*A*). The

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* Made by C. R. Bard, Inc., Summit, N. J.

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ARTIFICIAL KIDNEY: PRELIMINARY REPORT

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AND

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Since medicine began, doctors have been trying to devise ways and means of replacing the activity of the kidney, either by transplantation of that organ or by chemical means.

Regarding the former, it has been found impossible to transplant kidneys from one animal to another. The general experience has been that kidneys thus transplanted will appear to survive for a period of approximately 21 days, after which the transplanted organ acts as foreign protein and causes the death of the animal. A kidney can be successfully transplanted in an animal from its normal position in the loin to the pelvis, with an entirely new set of blood vessels; but it requires an autogenous transplant, as this does not hold true of a foreign kidney.

Methods of extracting retained waste products from the blood, in cases of kidney failure, have been fairly successful. It has been definitely shown that if the kidney can be tided over for a period of time by artificial means, that important structure may recuperate to such an extent that it will resume its activities and again become a satisfactorily functioning organ.

These methods are of two sorts. One is the lavage of various viscera. Under this head come duodenal lavage, developed by Dr. Joseph McCarthy in 1923, gastric lavage, intestinal irrigation, and the more recent and formidable peritoneal irrigation. The success attained by these methods in humans has been quite striking in some instances. On the other hand, there have been cases of complete anuria due to calculus, infection, the ingestion of cauterizing drugs, or occurring as a reflex after instrumentation in which the result has been complete failure.

The second method of extracting toxicity from the blood in kidney failure, and the one with which we are here concerned, is by mechanical means. A number of machines for the purpose of purifying the blood in lieu of kidney activity have been devised in recent years, and these will be reviewed briefly. Although not as yet widely employed, the artificial kidney has met with sufficient clinical success to show that, by its use, life can be prolonged during temporary acute renal insufficiency until recovery of renal function occurs.

The authors are here presenting a machine which is compact, efficient as a mechanical device, and satisfactory as regards treatment of the failing or collapsed kidney.

Read at annual meeting, American Urological Association, Washington, D. C., May 30, 1950.

depth of the penetration is indicated by the calibration on the shaft of the tube. In a child this distance is safely about 3 cm.; in a nonobese adult about 5 cm., and in an obese adult may be 10 cm. or more. With caution, gentleness and care, the bladder floor need not be scratched or injured.

Having introduced the trocar into the vesical cavity, the spear-pointed stylet is withdrawn and the well-lubricated catheter to be left indwelling is passed into the bladder through the opening on the side of the tube, the mechanics being that of a shoehorn or gorget (fig. 2). With the catheter introduced well into the bladder, the balloon is inflated and the trocar is withdrawn. For the comfort of the patient while he is wearing the catheter, it is important to keep its tip away from the trigone, vesical outlet or floor to avoid bladder irritation, spasm, or the reflexly produced desire to void. This is accomplished by withdrawing the catheter until it is stopped by the balloon, now in contact with the bladder dome. The catheter is anchored externally by a small piece of adhesive tape or other method and in a manner to keep the balloon closely approximated to the dome. A piece of gauze is applied to the small abdominal wound about the catheter to absorb moisture and serum; there are no sutures.

When the trocar is used for nephrostomy or pyelostomy the method of its introduction into the kidney pelvis is fundamentally the same as in cystostomy; the procedure is carried out on the exposed kidney or its pelvis respectively. In nephrostomy the parenchyma is penetrated at its palpably thinnest portion and preferably near the lower pole. When the loin wound has been closed, the catheter is gently withdrawn until it is felt to be withheld by the intrapelvic balloon and is anchored externally at this point as described under trocar cystostomy (fig. 3).

This instrument has been employed for these procedures in both adults and children; the youngest patient on whom trocar cystostomy was performed was 1 day of age. The trocar used in children is of 23F caliber as compared with the 26F employed in older patients. So simple is trocar cystostomy by this method that I can foresee its employment in some cases as an out-patient or office procedure. It is conceivable that this instrument and the indwelling balloon catheter might be employed in empyema and other intrapleural conditions requiring the establishment of tube drainage, or for the steps of tunnelling and emplacement of the free tube graft in the McIndoe operation for hypospadias.

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REVIEW OF THE LITERATURE

The development of the artificial kidney started with the work of Abel, Rowntree and Turner at The John Hopkins University in 1913. They conceived the idea that urea and other low molecular-weight components could be removed from the circulating blood of living animals by dialysis through a semipermeable membrane. The apparatus which they devised utilized collodion membranes prepared by dipping forms in a solution of cellulose nitrate. These membranes were immersed in saline solution, and arterial animal blood was passed through the device and returned to the venous system. Coagulation of the blood was prevented by the injection of hirudin, an extract of leeches. They referred to this process as "vivi-diffusion"; and for the apparatus which Abel described to the International Medical Congress that same year they coined the term "artificial kidney."

Stimulated by this work, George Haas, a German scientist, developed a dialyzing apparatus in 1915 which utilized collodion tubes encased in outer glass tubing. Blood was removed from the cubital vein and fractionally dialzyed for 30 minutes and then returned to the body. Hirudin, used as an anticoagulant, was found to produce unpleasant reactions and heparin was substituted. The procedure was slow and cumbersome, and the results were unsatisfactory. Haas did not publish his experimental results until 1925 and did not describe his apparatus until 1935.

Another artificial kidney was described in 1923 by Necheles, and further results were elaborated by Lims in 1927. Similar experiments were carried on by Nyiri in 1926.

The work of these pioneers had been seriously handicapped by the difficulties in preparing uniform dialyzing membranes and by the porosity of the prepared collodion membrane. The development by the chemical industry of cellophane in thin sheets of uniform thickness and the further refinement of heparin solved two of the major problems encountered by the earlier experimenters. Thalhimer in 1938 was the first to realize the tremendous advantages of these developments. He devised a dialyzer using cellophane tubing as a permeable membrane and immersed this in physiological salt solution. Heparinized blood was passed on the opposite side of the membrane and was then returned to the animal body.

The first artificial kidney suitable for clinical use was devised by W. J. Kolff of Kampen, Holland, in 1944. This apparatus, the result of extensive experimental and clinical tests, consisted of a large, cylindrical drum around which was wound spirally approximately 100 feet of one-inch cellophane tubing. The ends of the tubing were connected to rotating universal joints, and the entire drum was immersed in a large tub of solution containing various electrolytes. Blood was supplied to the tubing by arterial pressure and was returned to the venous system by means of a mechanical pump. More extensive reports of this apparatus and of his results were published by Kolff in 1946 and 1947.

The Kolff kidney was modified in England by Bywaters and later by Darmady, and in Canada by MacLean of Toronto and Palmer and Rutherford of Vancouver.

Early in 1947, Nils Alwall of Lund, Sweden, constructed an artificial kidney by winding cellophane tubing around a cylinder with provisions made for the inflow and outflow of blood. The cylinder was immersed in a large, cylindrical jar containing the electrolyte solution. Means were provided for agitation and temperature control of the solution. Later in the same year, Murray of Canada presented a dialyzer very similar to the Alwall unit.

Leonards and Skeggs in 1948 described an experimental dialyzer utilizing cellophane sheets as a permeable membrane.

The artificial kidneys described in the literature are of two types. One is the large circular drum, or Kolff type, kidney in which the drum containing the dialyzing membrane rotates in a large bath of electrolyte solution. This type of kidney has the disadvantages of excessive size, mechanical operating difficulties, and the possibility of leakage of blood through porous holes in the cellophane tubing. Such kidneys depend largely on arterial pressure to move the blood through the membrane. Less than one-half of the effective dialyzing area is utilized, inasmuch as only one-half of the area is immersed in the electrolyte solution at any one time.

Artificial kdineys of the second, or Alwall, type have many of the disadvantages of the rotating-type kidneys. They have small, cylindrical tanks of a limited electrolyte solution capacity. The cellophane tubing which is wound around a smaller cylinder has a limited dialyzing area and is subject to the same occasional difficulties, such as leakage due to porosity and the necessity for changing the small volume of electrolyte solution several times during the period of dialysis.

GENERAL PRINCIPLES OF THE LOWSLEY-KIRWIN ARTIFICIAL KIDNEY

In developing the Lowsley-Kirwin artificial kidney, we attempted to eliminate the physical and mechanical difficulties inherent in the previous machines, and to construct a small, compact unit having maximum effective dialyzing surface, a completely self-contained unit with the capacity for enough electrolyte solution for complete dialysis and equipped with temperature control, circulating mechanisms, meters for the measurement of the rate of flow of blood and of dialyzing solution, and an adequate blood pump capable of removing blood from the venous system without destroying the cellular components of the blood (figs. 1, 2, 3, 4). We have utilized the modern principles of dialysis which have been employed in large-scale industrial and scientific operations during recent years. Cellophane sheets have been used as permeable membranes instead of the cellophane or collodion tubing heretofore used in other kidneys. With modern methods, it is possible to produce a uniform, homogeneous cellophane sheet free from pinholes or porous sections.

Two types of kidneys have been prepared: 1) a parallel counter-current flow type, and 2) a series counter-current flow type.

In the *parallel counter-current flow type of kidney* the blood and electrolyte cells are separated by circular sheets of cellophane mounted on transparent plastic supports, and are arranged alternately, with the blood chambers interspersed between pairs of water chambers. In this system, the blood is pumped through a common header at the base of the dialyzer and rises through the blood chambers, flowing over the permeable membrane and leaving the chamber at the top through a common header. The electrolyte solution enters the water chambers through a common header at the top of the dialyzer and passes downward over the permeable membrane on the side opposite the blood, in a counter-current direction, discharging from a common header at the bottom.

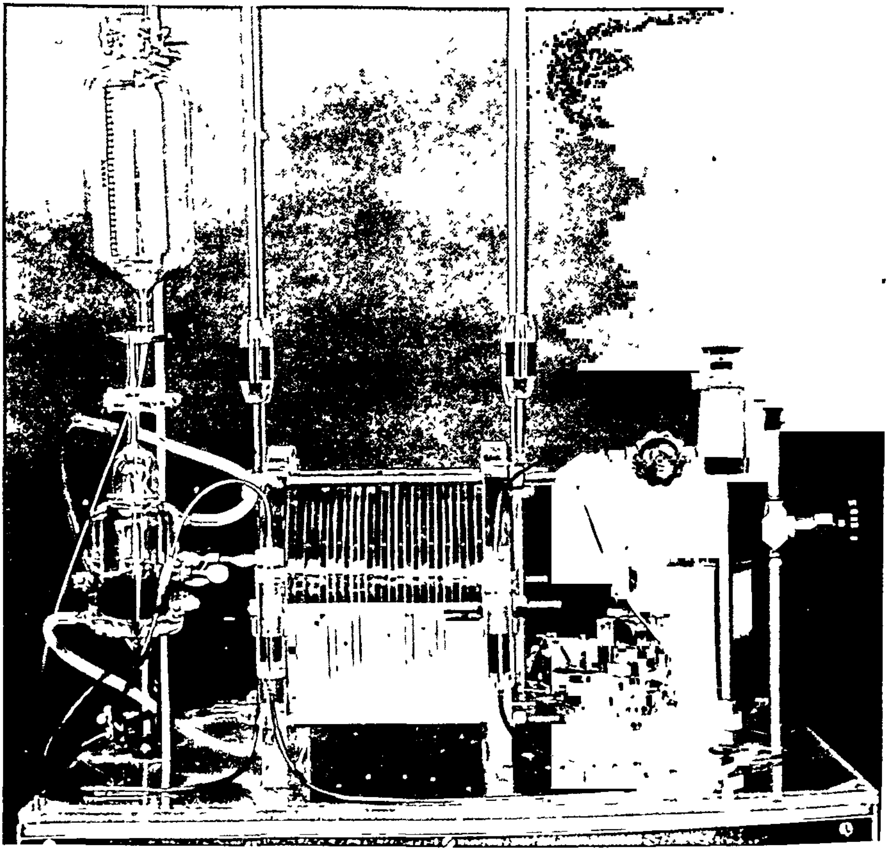

Fig 1. Lowsley-Kirwin artificial kidney Counter-current parallel flow artificial kidney: dialyzer

In the *series counter-current flow type of kidney* each cell consists of a chamber in which is mounted a circular or rectangular sheet of cellophane. The plastic surfaces of the chambers are serrated on opposite sides to permit the flow of blood on one side and the flow of water on the other side, with the serrations arranged in such a manner that the direction of the flow of blood and water is counter-current. The blood enters the first chamber and, after passing over the permeable membrane, enters the second chamber and alternates through the remaining dialyzing chambers until it exits from the last chamber. The electrolyte solution enters the last chamber first and flows in a counter-current manner through the consecutive dialyzing chambers and exits at the first chamber. This type of construction gives very high dialyzing efficiencies.

IN VITRO TESTS

A large series of in vitro tests was made, using aqueous solutions of urea under various conditions, in order to determine the effect of the rate of flow of urea and electrolyte solution, the concentration of urea, and the thickness of the dialyzing membrane on the rate of removal of urea from aqueous solutions; also the effective dialyzing area, effective pressure, the rate of urea removal in animal and human blood solutions, and the effect of the above-mentioned variables on the parallel flow and series flow type of artificial kidney respectively.

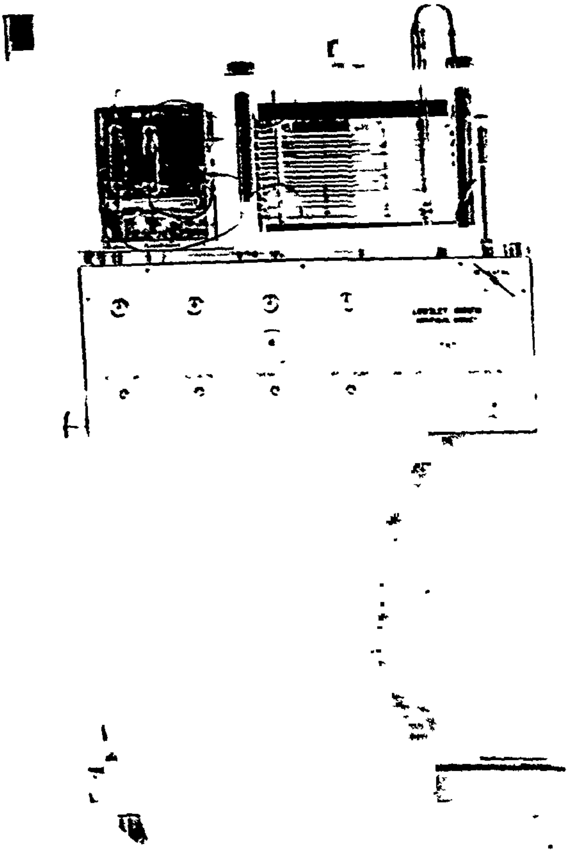

FIG. 2. Counter current series flow artificial kidney

The results indicated that urea can be effectively reduced in a period of 6 hours in a parallel flow system. The rate of removal was not significantly influenced by increasing the flow ratio of water to urea solution.

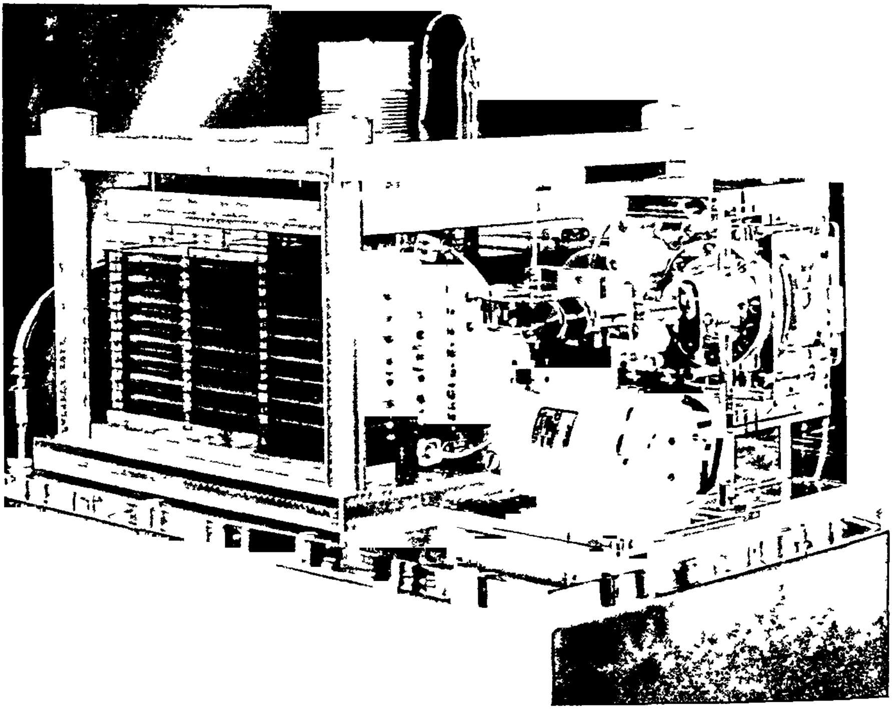

FIG 3 Counter-current series flow artificial kidney dialyzer

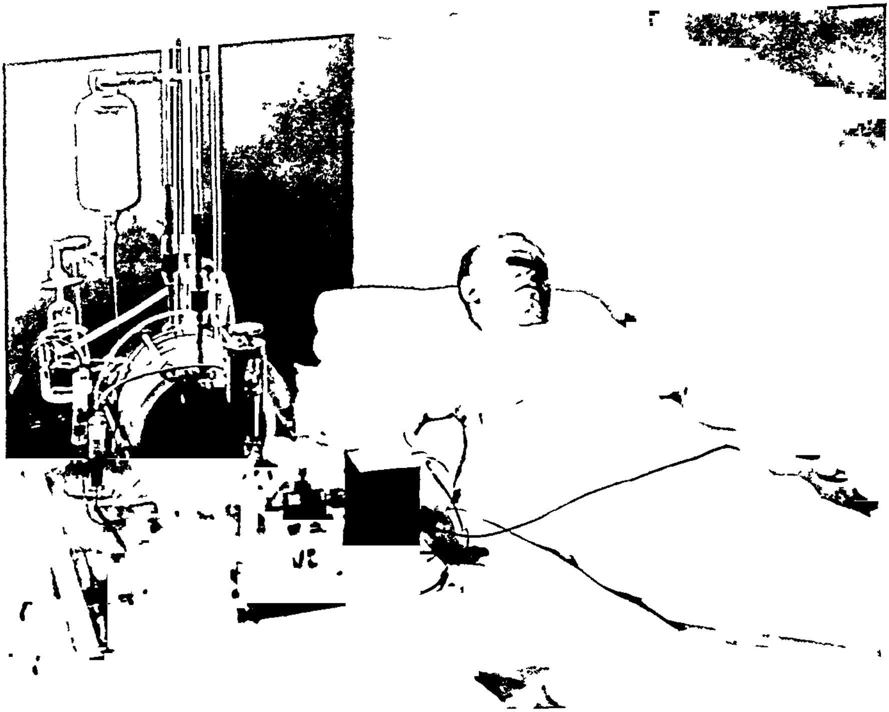

FIG 4 Counter-current parallel flow artificial kidney in use on a patient

1) The rate of removal of urea in aqueous solutions, using a counter-current parallel flow type of artificial kidney and utilizing an effective dialyzing area of 462 square inches, was studied. The flow rate on the water side of the kidney was varied in ratios of 4:1, 16:1 and 39.6:1. Urea solution containing 250 mg. per cent urea was used in a quantity approximately equivalent to the normal blood volume of the human. The results listed in table 1 show that the urea is effectively removed in this volume of solution in a period of 6 hours in a parallel flow system, and that the rate of removal of urea was not significantly influenced by increasing the flow ratio of water to urea above a ratio of 4:1.

TABLE 1. *Removal of urea from aqueous solutions*
Parallel Flow Type Artificial Kidney—Dialyzing Area 462 Square Inches

DIALYSIS	FLOW RATE 4:1	FLOW RATE 16:1	FLOW RATE 39.6:1
	Urea Con	Urea Con.	Urea Con
Hours	*Mg. %*	*Mg. %*	*Mg. %*
0	250	250	250
1	208	193	177
2	150	114	107
3	103	77	75
4	67	53	47
5	49	32	32
6	35	20	25

TABLE 2 *Effect of membrane thickness on rate of urea removal*
Parallel Flow Type Kidney—Flow Ratio 16:1

DIALYSIS	MEMBRANE THICKNESS		
	300 (.001 inch)	450 (.0015 inch)	600 (.002 inch)
Hours	*Mg. %*	*Mg. %*	*Mg. %*
0	250	250	250
1	178	168	165
2	108	90	158
3	65	43	118
4	47	25	96
5	34	13	75
6	31	5	70

2) The effect of the thickness of the dialyzing membrane on the rate of removal of urea in the parallel flow type of kidney was studied. In these experiments the flow ratio of water to urea solution was maintained at 16:1. The results outlined in table 2 indicate that the rate of removal of urea from aqueous solutions is higher when thin membranes are used—that is, a dialyzing membrane having a thickness of less than .001 inch.

3) A series of tests was undertaken to determine the rate of removal of urea from aqueous solutions, using a counter-current series flow type of artificial kidney and utilizing an effective dialyzing area of 720 square inches and a flow rate of aqueous urea solution of 100 cc per minute. The ratio of water flow to urea flow was maintained at 10:1. The results listed in table 3 indicate that urea

concentration can be reduced from 250 mg. per cent to 18 mg. per cent within a period of 50 minutes.

4) The effect of urea concentration on urea removal in aqueous solutions per single passage through a series flow type of kidney was studied. The results outlined in table 4 indicate that the per cent of urea removed increases with the concentration of urea, and that the higher the concentration of urea the greater the amount removed.

5) The effect of the rate of flow of animal blood per single passage through a series flow dialyzer on the urea concentration was studied. Urea was added to animal blood to give a concentration of 873 mg. per cent and heparin was used as an anticoagulant. The blood flow rate was varied through the kidney from 220 cc per minute to 40 cc per minute. The results outlined in table 5 indicate that, to approach the normal functions of the human kidney, the artificial kidney must function at blood rates of from 100 to 220 cc per minute, and that under these conditions the ratio of the water or electrolyte solution flow to the blood flow should be not less than 5:1.

TABLE 3. *Removal of urea from aqueous solution*
Series Flow Type Artificial Kidney

DIALYSIS	UREA	PER CENT OF ORIGINAL CONCENTRATION REMOVED
Minutes	*Mg. %*	
0	250	
5	226	9.6
10	203.5	18.6
15	182	27.2
20	160	36.0
25	137	45.2
30	113	54.8
35	89.5	64.2
40	65	74.0
45	41	83.6
50	18	92.8

TABLE 4. *Effect of urea concentration on urea removal*
Per Single Passage Through Series Flow Type Artificial Kidney

UREA MG % INPUT	UREA MG. % EXHAUST	PER CENT OF UREA REMOVED
45	19	76
156	51	67
169	40	76
246	52	78
426	70	83

DESCRIPTION OF LOWSLEY-KIRWIN ARTIFICIAL KIDNEY

On the basis of the experimental data developed in the in vitro tests, an artificial kidney suitable for use on humans was designed. Adequate provisions were made for the maintenance of high blood flow rates and suitable water flow rates.

The initial machine, which was used in the in vivo tests on animals and in clinical applications to humans, utilized a counter-current parallel flow type of dialyzing unit. The body of the machine consisted of a rectangular stainless steel tank which was mounted on roller-bearing casters. The tank was compartmented, the bottom section holding approximately 38 gallons of electrolyte solution. An outlet valve was provided in the bottom for drainage of the tank after use, and an inlet valve for the addition of components of the electrolyte solution. Facilities were provided for emptying the tank through the drainage valve, or by means of the circulating pump. The base of the tank was equipped with an agitator, a temperature control mechanism, and a pump for transferring the electrolyte solution from the tank to the dialyzer.

The dialyzer itself, of the parallel flow type, had 13 chambers for blood and 12 alternate chambers for electrolyte solution. This unit was equipped with meters for indicating the rate of flow of blood and a clot trap for the removal of air-bubbles and clots on the discharge end of the dialyzer.

A mechanism for adjusting the internal pressure of water and electrolyte solutions was mounted on top of the dialyzing tank. A special type of blood pump was designed to prevent the destruction of the cellular components of the blood. This consisted of a pulsating diaphragm equipped with two small butterfly valves to prevent back-flow. Means were provided in the pump to increase or decrease the rate of flow.

TABLE 5. *Effect of rate of flow of blood on urea removal per single passage through series flow type artificial kidney*

FLOW RATE BLOOD	UREA INPUT	UREA REMOVED	CLEARANCE BLOOD
cc/min.	*Mg. %*	*Mg. %*	*cc/min.*
220	873	317	80
180	873	341	70
100	873	411	47
40	873	533	24

In preparing the Lowsley-Kirwin artificial kidney for operation, the tank is first filled with ordinary tap water to which are added electrolytes in measured quantities. The electrolyte solution used in the majority of the tests consisted of the following:

	gm.
Potassium chloride	58
Sodium chloride	870
Dextrose	2175
Sodium bicarbonate	290

These quantities added to 38 gallons of water produce a solution of the following concentration:

	per cent
Potassium chloride	0.04
Sodium chloride	0.6
Dextrose	1.5
Sodium bicarbonate	0.2

The machine is assembled prior to use, the time required being approximately 30 minutes. All of the lines which come in contact with blood, including the pump and the blood chambers of the dialyzing unit, are disinfected by soaking in cold aqueous urolocide solution for a period of 16 hours. This is usually accomplished by assembling the artificial kidney and filling it with disinfecting solution the evening preceding the application of the machine to the patient.

ANIMAL EXPERIMENTS

A number of preliminary experiments were performed on dogs for the purpose of developing a standard technique which would be best suited to the living subject, and also to orient personnel in the use and operation of the machine. In the animal experiments a modified version of the machine was used. This consisted of about one-third of the dialyzing chambers, corresponding approximately to the dog's weight as related to the weight of the human.

Isolation of the femoral vein was performed on anesthetized dogs. After a suitable time, to allow for clotting at the cut-down site, the animals were heparinized and the veins cannulated with polyethylene tubing. Considerable difficulty was encountered by not securing an adequate flow of blood from the animal due to occasional collapsing of the veins against the cannular eye, inadequate blood supply to the cannulas, and premature coagulation. It was necessary to establish a heparin tolerance test curve for each animal to be dialyzed, permitting evaluation of the thrombophilic tendency of the particular animal and determination of the amount and frequency of administration of heparin.

TABLE 6. *Results of dialysis, dog No. 4*

DIALYSIS	BLOOD UREA NITROGEN
Hours	*Mg. %*
Start	345
1	281
2	244
3	220

Urea removed by artificial kidney.......................................11.9 gm.
Urea removed by dog's kidney...11.15 gm.

The results obtained during the dialysis of one of the many dogs used in the experimental work are outlined in table 6. In this experiment the femoral vein was isolated and cannulated and the dog was heparinized. The urea level of the animal was increased by the addition intravenously of 55 grams of urea in aqueous solution. Prior to the administration of the urea solution, the dog's bladder was emptied completely of urine. After 30 minutes, the blood urea level of the animal was determined to be 345 mg. per cent. The animal was connected to the artificial kidney and dialysis continued for a period of 3 hours. The blood urea was reduced from 345 mg. per cent to 220 mg. per cent. A total of 11.9 gm. urea was removed by the dialyzer. The urine in the dog's bladder was then evacuated, and urea determinations showed that 11.15 gm. urea had been re-

moved by the dog's kidney, indicating that the artificial kidney more than matched the dog's on a gram-for-gram basis of urea removed.

UTILIZATION OF THE ARTIFICIAL KIDNEY IN HUMANS

The animal experiments demonstrated that the machine was suitable for application to human patients.

In using the artificial kidney on humans, some precautionary measures are necessary. Most workers in the field of hemodialysis have been opposed to treating patients with poor cardiac reserve. We have taken exception to this by dialyzing some patients with mild decompensation, without ill effect. In cases of cardiac decompensation, it has been the policy to digitalize the patient fully prior to dialysis, the rate of digitalization being determined by the emergent nature of the uremia.

The preliminary heparin tolerance test is necessary to determine individual patient variations in metabolism. This test is performed by injecting 1 mg. heparin per kilo of body weight intravenously and plotting the rise in the clotting time and the gradual fall of the clotting time as the heparin metabolizes. Routinely, an initial dose of 1 mg. heparin per kilo of body weight is given, followed by additional intravenous injections of heparin every 30 minutes during dialysis. If the heparin tolerance test shows resistance of heparin, it is sometimes necessary to increase the amounts and the frequency of administration.

Calcium must be supplied to the patients in the form of calcium gluconate administered intravenously. This is necessary where electrolyte solutions which contain no calcium are used. Calcium can be used in the electrolyte solution provided the partial pressure of carbon dioxide is maintained in the solution to prevent precipitation of the solution as an insoluble salt. Excessive doses of intravenous calcium should not be administered to digitalized patients.

The best results in maintaining adequate blood flow are obtained with deep cannulation of the anticubital veins, inserting the largest bore of thin-walled polyethylene tubing that the vein will accommodate.

No preliminary medication other than a sedative dose of barbiturate is necessary. The patients were found to suffer little discomfort during the dialysis. We consider it advisable to utilize the artificial kidney for a period of 1 to 4 hours and then give the patient a period of rest before continuing its use.

Little variation was observed in blood pressure readings, which were taken regularly during the dialysis. Careful control is maintained over the input and output, to keep the average variation to less than 10 mm. of mercury between the start and finish. No evidence of hemolysis was observed during or after dialysis. Laboratory tests showed no free hemoglobin in the serum or the urine of the patients dialyzed. The patients experienced no unpleasant post-dialysis reactions, such as chills or temperature elevation.

Immediate symptomatic relief was experienced in 2 cases.

Sodium and potassium levels were controlled by adjusting the concentration of these components in the electrolyte solution. It is possible by means of the

The machine is assembled prior to use, the time required being approximately 30 minutes. All of the lines which come in contact with blood, including the pump and the blood chambers of the dialyzing unit, are disinfected by soaking in cold aqueous urolocide solution for a period of 16 hours. This is usually accomplished by assembling the artificial kidney and filling it with disinfecting solution the evening preceding the application of the machine to the patient.

ANIMAL EXPERIMENTS

A number of preliminary experiments were performed on dogs for the purpose of developing a standard technique which would be best suited to the living subject, and also to orient personnel in the use and operation of the machine. In the animal experiments a modified version of the machine was used. This consisted of about one-third of the dialyzing chambers, corresponding approximately to the dog's weight as related to the weight of the human.

Isolation of the femoral vein was performed on anesthetized dogs. After a suitable time, to allow for clotting at the cut-down site, the animals were heparinized and the veins cannulated with polyethylene tubing. Considerable difficulty was encountered by not securing an adequate flow of blood from the animal due to occasional collapsing of the veins against the cannular eye, inadequate blood supply to the cannulas, and premature coagulation. It was necessary to establish a heparin tolerance test curve for each animal to be dialyzed, permitting evaluation of the thrombophilic tendency of the particular animal and determination of the amount and frequency of administration of heparin.

TABLE 6. *Results of dialysis, dog No. 4*

DIALYSIS	BLOOD UREA NITROGEN
Hours	*Mg. %*
Start	345
1	281
2	244
3	220

Urea removed by artificial kidney	11.9 gm.
Urea removed by dog's kidney	11.15 gm.

The results obtained during the dialysis of one of the many dogs used in the experimental work are outlined in table 6. In this experiment the femoral vein was isolated and cannulated and the dog was heparinized. The urea level of the animal was increased by the addition intravenously of 55 grams of urea in aqueous solution. Prior to the administration of the urea solution, the dog's bladder was emptied completely of urine. After 30 minutes, the blood urea level of the animal was determined to be 345 mg. per cent. The animal was connected to the artificial kidney and dialysis continued for a period of 3 hours. The blood urea was reduced from 345 mg. per cent to 220 mg. per cent. A total of 11.9 gm. urea was removed by the dialyzer. The urine in the dog's bladder was then evacuated, and urea determinations showed that 11.15 gm. urea had been re-

moved by the dog's kidney, indicating that the artificial kidney more than matched the dog's on a gram-for-gram basis of urea removed.

UTILIZATION OF THE ARTIFICIAL KIDNEY IN HUMANS

The animal experiments demonstrated that the machine was suitable for application to human patients.

In using the artificial kidney on humans, some precautionary measures are necessary. Most workers in the field of hemodialysis have been opposed to treating patients with poor cardiac reserve. We have taken exception to this by dialyzing some patients with mild decompensation, without ill effect. In cases of cardiac decompensation, it has been the policy to digitalize the patient fully prior to dialysis, the rate of digitalization being determined by the emergent nature of the uremia.

The preliminary heparin tolerance test is necessary to determine individual patient variations in metabolism. This test is performed by injecting 1 mg. heparin per kilo of body weight intravenously and plotting the rise in the clotting time and the gradual fall of the clotting time as the heparin metabolizes. Routinely, an initial dose of 1 mg. heparin per kilo of body weight is given, followed by additional intravenous injections of heparin every 30 minutes during dialysis. If the heparin tolerance test shows resistance of heparin, it is sometimes necessary to increase the amounts and the frequency of administration.

Calcium must be supplied to the patients in the form of calcium gluconate administered intravenously. This is necessary where electrolyte solutions which contain no calcium are used. Calcium can be used in the electrolyte solution provided the partial pressure of carbon dioxide is maintained in the solution to prevent precipitation of the solution as an insoluble salt. Excessive doses of intravenous calcium should not be administered to digitalized patients.

The best results in maintaining adequate blood flow are obtained with deep cannulation of the anticubital veins, inserting the largest bore of thin-walled polyethylene tubing that the vein will accommodate.

No preliminary medication other than a sedative dose of barbiturate is necessary. The patients were found to suffer little discomfort during the dialysis. We consider it advisable to utilize the artificial kidney for a period of 1 to 4 hours and then give the patient a period of rest before continuing its use.

Little variation was observed in blood pressure readings, which were taken regularly during the dialysis. Careful control is maintained over the input and output, to keep the average variation to less than 10 mm. of mercury between the start and finish. No evidence of hemolysis was observed during or after dialysis. Laboratory tests showed no free hemoglobin in the serum or the urine of the patients dialyzed. The patients experienced no unpleasant post-dialysis reactions, such as chills or temperature elevation.

Immediate symptomatic relief was experienced in 2 cases.

Sodium and potassium levels were controlled by adjusting the concentration of these components in the electrolyte solution. It is possible by means of the

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artificial kidney to not only remove electrolytes such as sodium or potassium, but to add to these electrolytes in the blood by increasing their concentration in the solution.

The average blood urea nitrogen in all patients at the start of the dialysis was 130 mg. per cent, and after 3 hours dialysis was 99 mg. per cent.

The results obtained on 1 patient are listed in table 7.

TABLE 7. *Results of dialysis in human patient, case M. F.*

DIALYSIS	UREA NITROGEN	NONPROTEIN NITROGEN	CREATININE
	Mg. %	*Mg. %*	*Mg. %*
Start	165	212.5	17.4
3 Hours Dialysis	75	115	3
72 Hours after Dialysis	9	35	1.6

SUMMARY AND CONCLUSIONS

A new artificial kidney is presented which is compact, mechanically efficient, and satisfactory as regards treatment of the failing or collapsed kidney.

This machine has the following advantages over artificial kidneys previously described:

1) It is relatively small and may easily be moved into any patient's room.

2) Its parts are satisfactorily sterilized at the present time by immersion in an antiseptic solution such as cold aqueous urolocide solution, and ultimately it will be so constructed that it will be possible to autoclave the entire unit.

3) The heparinized blood of the patient is removed from the venous system and moved through the dialyzer by an efficient mechanical pump at an appropriate and readily controlled rate of flow, and the volume of blood which is contained in the dialyzer, in series, is only 300 cc. The electrolyte solution is at all times maintained at a suitable temperature which is controlled by a thermostat in the machine.

4) It is not necessary to change the electrolyte solution, which may be used over and over again during the period of dialysis.

5) It is possible not only to remove electrolytes such as sodium or potassium, but, if desired, to add to these electrolytes in the blood by increasing their concentration in the electrolyte solution.

The use of this dialyzer in vitro, in experimental animals, and in humans is described and the results summarized.

It is concluded from our experience with this machine that low molecular nitrogenous products are effectively removed from aqueous solutions.

Animals poisoned in a fashion to bring about uremia are satisfactorily treated.

A limited use on humans has proven it to be an efficient substitute for the kidney for various lengths of time.

From experience to date, the artificial kidney appears to be most valuable in cases of renal failure in which there is some hope that the kidneys may regain adequate function within a fairly limited time. This would include patients suffering from extreme oliguria or anuria caused by calculus, chemical poisoning by bichloride of mercury, phenol, etc., incompatible blood transfusions, sulfonamide toxicity, pregnancy toxemia, severe burns, a crushing injury (crush syndrome), surgical injury to the urinary tract (such as accidental severance or ligation of the ureters), mechanical obstruction in any part of the urinary tract which prevents the outflow of urine from the kidneys, or anuria occurring as a reflex following instrumentation. It should also be valuable in certain cases of exacerbations in chronic renal disease.

Our experience is not sufficiently great to indicate how long one may utilize this machine effectively before the patient's kidneys will have to be relied upon to do the work required.

We consider it advisable to dialyze the patient for 4 or 6 hours and then give him an equal period of rest before continuing treatment, due to the necessity of keeping the arms in one position during the dialysis. If the patient is in a coma, however, the use of the dialyzer may be continuous.

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REFERENCES

ABEL, J. J.: Plasma removal with return of corpuscles (plasmaphaeresis). J. Pharmacol., 5: 625, 1913.

ABEL, J. J., ROWNTREE, L. G. AND TURNER, B. B.: On the removal of diffusible substances from the circulating blood of living animals by dialysis. J. Pharmacol. & Exper. Therap., 5: 275, 1913–14.

ALWALL, N.: On the artificial kidney. Apparatus for dialysis of the blood in vivo. Acta med. Scandinav., 128: 317, 1947.

ALWALL, N.: Clinical extracorporeal dialysis of blood with an artificial kidney. Lancet, 1: 60, 1948.

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BYWATERS, E. G. L. AND JOEKES, A. M.: The artificial kidney: its clinical application in the treatment of traumatic anuria. Proc. Roy. Soc. Med., 41: 420, 1948.

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HAAS, G.: Die methodik der blutauswashung (dialysis in vivo). Aberhaldens Handbuch der Biologischen Arbeitsmethoden, 5: 717, 1935.

KOLFF, W. J.: The artificial kidney. Monograph, Kampen, Holland: J. H. Kok, 1946.

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REFERENCES

Abel, J. J.: Plasma removal with return of corpuscles (plasmaphaeresis). J. Pharmacol., 5: 625, 1913.

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Alwall, N.: Clinical extracorporeal dialysis of blood with an artificial kidney. Lancet, 1: 60, 1948.

Alwall, N. and Norvitt, L.: On artificial kidney: effectivity of apparatus. Acta med. Scandinav., supp. 196, p. 250, 1947.

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Darmady, E. M.: Dialysis of the blood for the treatment of uremia. Proc. Roy. Soc. Med., 41: 418, 1928.

Haas, G.: Die methodik der blutauswashung (dialysis in vivo). Aberhaldens Handbuch der Biologischen Arbeitsmethoden, 5: 717, 1935.

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Kolff, W. J.: New Ways of Treating Uremia. London: J. and A. Churchill, 1947.

Kolff, W. J.: The artificial kidney. J. Mt. Sinai Hosp., 14: 71, 1947–48.

Kolff, W. J. and Berk, H. T. J.: Artificial kidney; dialyzer with great area. Acta med. Scandinav., **117**: 121, 1944.

MacLean, J. T., Ripstein, C. B., deLeeuw, N. K. M. and Miller, G. G.: The use of the artificial kidney in the treatment of uremia. Canad. M.A.J., **58**: 433, 1948.

Murray, G.: Development of an artificial kidney. Arch. Surg., **55**: 505, 1947.

Murray, G., Delorme, E. and Thomas, N.: Artificial kidney. J.A.M.A., **137**: 1596, 1948.

Necheles, H.: Ueber dialysieren des stromenden blutes am lebenden. Klin. Wchnschr., **2**: 1257, 1888, 1923.

Nyiri, W.: Experimental untersuchungen ueber gekreuzte bluttransfusion bei uramie. Arch. f. Pathol. u. Pharm., **116**: 117, 1926.

Palmer, R. A. and Rutherford, P. S.: Kidney substitutes in uremia: use of Kolff's dialyser in two cases. Canad. M.A.J., **60**: 261, 1949.

Skeggs, L. T. and Leonards, J. R.: Studies on an artificial kidney: Preliminary results with a new type of continuous dialyzer. Science, **108**: 212, 1948.

Sterling, J. A. and Doane, J. C.: A new type of artificial kidney. Urol. & Cutan. Rev., **53**: 385, 1949.

Thalhimer, W.: Experimental exchange transfusion for reducing azotemia. Use of artificial kidney for this purpose. Proc. Soc. Exper. Biol. & Med., **37**: 641, 1938.

Thalhimer, W., Solandt, D. L. and Best, C. H.: Experimental exchange transfusion using purified heparin. Lancet, **2**: 554, 1938.

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UROLOGICAL SURVEY OF ANURIA AND OLIGURIA WITH A GUIDE TO TREATMENT

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In light of present knowledge of the structure and function of the nephron with its multiple component parts, intricate vascular system and diversified function, and in view of better understanding of biochemical relationships and acid-base equilibrium in the human body, some revision in the urologist's conception of that state characterized by oliguria and anuria seems pertinent.

According to Oliver,[1] great confusion exists in the interpretation of terms describing kidney failure such as uremia, extrarenal uremia, pre-renal uremia, renal uremia, post-renal uremia, lower nephron nephrosis and nephrotic episodes in general. These terms do not accurately describe the state of the kidney in 'uremic' disease but should be replaced on a basis of morphological change with alteration of function of the nephron leading to oliguria and anuria.

Our interest in the subject stems from some experimental work performed by Arcadi and Farman[2] (1949) on the influence of varying states of hydration and a few drugs on the vascular pathways of the kidney. Water diuresis and magnesium sulfate (of the strength, 50 per cent, used in eclampsia) tend to concentrate the blood in the cortical circuit whereas dehydration in rabbits diverts the blood flow to the medullary circulation. Trueta and associates[3] (1947) have proven beyond doubt that two potential circulations exist within the kidney. It was shown that the blood flowing through the kidneys has two routes which it may take, and depending on the particular conditions, may flow by one or the other of the routes. It also may flow through each simultaneously. These two "potential" routes involve cortical and medullary vascular circuits in the kidney. It was shown that this phenomenon by which the blood is shunted either into the cortex or into the medulla (into the large juxtamedullary glomeruli) is mediated through the nerve supply of the kidney. Oliver[1] recognizes the pathway for such a 'shunt' but states that it is not clear under what conditions it actually operates in man.

PATHOGENESIS

An understanding of the mechanism by which oliguria and anuria are produced is necessary for classification (working diagnosis), localization of the nephron lesion and institution of rationale treatment. The three leading morphological factors in 'anuric' pathogenesis attained so far from experimental and clinical evidence may be said to be:

1) Vasospasm of the interlobular arteries and arterioles supplying the glo-

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Read at annual meeting, American Urological Association, Washington, D. C., May 31, 1950

[1] Oliver, J.: When is a kidney not a kidney? J. Urol., 63: 373–402, 1950.

[2] Arcadi, J. and Farman, F.: Experimental studies and clinical aspects of the renal circulation. J. Urol., 62: 756–761, 1949.

[3] Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J. and Prichard, M. M. L.: Studies of the renal circulation., Springfield, Ill.: Charles C Thomas, 1947.

merulus and tubular system. This leads primarily to cortical ischemia and anoxia, diminished blood flow and volume, and consequently diminished glomerular filtrate.

2) Alterations in the function of the proximal tubules, greater reabsorption of fluids, altered interchange of metabolites or in cases of complete destruction of the epithelium, no function at all. Selective activity of segments of the tubules indicates that the influence of toxic (nephrotoxic) factors is greatest in the proximal convolutions.

3) Blockage of the distal tubules by casts, heme pigment, compression (interstitial edema), and pressure deformities of the nephron all lead to rapid alteration of the epithelium in which the mechanical factor is an important pathogenic cause. Further blockage or obstruction in the collecting tubules, as by precipitated acetyl sulfonamide crystals and back pressure from lower urinary tract obstruction are important factors leading to retrograde dilatation of the entire nephron and cessation of secretion.

The question of reversible action, or as some prefer to say, restoration of function, from a theoretical viewpoint depends to a large extent upon the type and severity of the nephron change. Vasoconstriction of the glomeruli arterioles and mechanical blockage of the distal and collecting tubules yield most readily to our present methods of therapy. Also early oliguria due to altered permeability of the epithelial cells in the proximal tubules is reversible if the toxic factor is not overwhelming or if combated properly by regulation of fluid balance, metabolite neutralization, and nutritional maintenance. The more non-reversible conditions are extensive epithelial destruction in the proximal tubules and unrecognized or improperly treated renal ischemia. The time factor here is important. Treatment must be instituted and uremic toxic conditions combated before complete and irreversible tubular epithelial destruction or necrosis due to anoxia takes place.

Another important consideration In diagnosis and prognosis is recognition of whether the kidney has been damaged previously by chronic renal disease. Is the anuria the result of an acute process in an otherwise normally functioning kidney? In the 'crush syndrome' in young subjects it may be assumed that the kidneys were normal beforehand, but in oliguria occurring following transurethral operation or in post-surgical patients the kidney function may have been previously altered as by chronic pyelonephritis. A careful history of what has gone on before is important. Cubitt[4] (1937) laments the fact that case records are notably lacking in certain details which might have indicated a possible path toward solution. Previous infectious diseases, the association of septicemia, the rapid onset of emergencies and the difficulty of investigation in patients gravely ill all add to the difficulty of determining etiological factors.

ETIOLOGY

Of 'kidney failure' diseases which interest the urologist most may be mentioned pyelonephritis, muscle trauma (crush syndrome), sulfonamide intoxication, intravascular hemolysis, concealed hemorrhage, hemoglobinuria, prolonged shock, toxemias of pregnancy or abortion, and lower urinary tract obstruction. Lucké,[5] Mallory,[6] Daugherty and Odel,[7] Humphrey and Jones,[8] and others list burns, heat stroke, poisoning with chemical or vegetable agents or with heavy metals, malarial hematuria (blackwater fever), Weil's disease (acute infectious jaundice), acute glomerulonephritis, infectious hepatitis, pyloric stenosis, biliary tract operations, infantile diarrhea, symmetrical cortical necrosis, excessive vomiting, and alkalosis from any cause as etiological factors in the production of oliguria and anuria.

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[4] Cubitt, A. W.: The problem of anuria. A review of recent work on renal physiology with reports of 2 cases. Brit. J. Surg., 24: 1936–April 1937.

It is interesting to note that in symmetrical cortical necrosis of the type following abortion, the principal changes found in the kidney are cellular necrosis (distal tubules), intersititial edema and polymorphonuclear infiltration, a finding which corresponds closely to altered structure of the lower nephron following severe trauma. Oliguria occurs in each and the cessation of secretion is believed primarily due to obstructive ischemia resulting from vasospasm of the interlobular arteries and arterioles (Christian).[9] O'Donnell[10] has reported three fatal cases and observes that the symmetrical cortical necrosis of late pregnancy may be but a more severe stage of lower nephron nephrosis. Humphrey and Jones[8] (1947) have reported 4 cases of extreme post-abortal oliguria, all of which recovered with conservative treatment. Of the medullary lesions producing anuria, papillary necrosis or necrotizing renal papillitis is the most graphic example. Some cases of unexplained hemoglobinuria with diminished urinary output may be explained on the basis of severe chronic pyelonephritis with terminal necrotizing renal papillitis.

We have reclassified our own cases of uremia and anuria on the basis of known etiological factors and have arbitrarily attempted to localize the principal nephron lesion in order to understand future 'kidney failure' problems and to institute improved methods of therapy (table 1).

In 35 cases of acute uremia characterized by partial or complete suppression of urine, 24 were associated with chronic renal disease usually referred to as some form of nephritis. Of these chronic renal lesions 6 recovered or approximately one-fourth. There are 9 cases in group 1 in which the primary nephron lesion has been placed in the proximal tubules, and of these only one recovered (about 10 per cent). It may be judged that the mortality rate in acute lesions of the upper nephron is extremely high (near 90 per cent), which bears out clinical experience in cases of poisoning by heavy metals (bichloride of mercury) and tubular damage following abortion of eclampsia in which the toxic factor is paramount.

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[5] Lucké, B.: Lower nephron nephrosis (the renal lesions of the crush syndrome, of burns, transfusions, and other conditions affecting the lower segments of the nephrons). Mil. Surg. 99: 371, 1946.

[6] Mallory, T. B.: Hemoglobinuric nephrosis in traumatic shock. Amer. J. Clin. Path. 17: 427, 1947.

[7] Daugherty, G. W. and Odel, H. M.: Management of acute renal insufficiency. Modern Medicine, pp. 55–56, February 1, 1950.

[8] Humphrey, J. H. and Jones, A.: Oliguria after abortion. Clin. Sci, 6: 173–186, 1947.

[9] Christian, H. A.: Bright's Disease. New York: Oxford University Press, 1948, 385 pp.

[10] O'Donnell, W. M.: Postabortal oliguria. J.A.M.A., 140: 1201, 1949.

In group 2 there are a total of 18 cases or twice the number as in group 1. These primarily include etiological causes such as lower urinary tract obstruction, incompatible blood transfusion and blockage of the distal tubules with acetyl sulfonamide crystals. The recovery rate also is higher (38.9 per cent) and it is with this group that the urologist mostly is concerned.

Group 3 includes cases of post-surgical shock, concealed hemorrhage (renal rupture) and 'reflex anuria' as from sudden impacted ureteral calculus. Primarily the quickly developing anuria is the result of vasoconstriction of the arterioles supplying the cortical glomeruli. Recovery rate in this group was 37.5 per cent. *Immediate treatment primarily is that of shock and release of all neurogenic influence.* The general surgeon may encounter cases in this group.

CLINICAL PICTURE

The renal insufficiency which ensues with the foregoing conditions develops along similar patterns producing recognizable symptoms, but there are differentiating points which depend primarily upon the nephron segment involved. In disturbance of the distal tubules (lower nephron nephrosis) some degree of shock, oliguria or anuria, rising nonprotein nitrogen, hypertension, vomiting, edema, proteinuria and abnormal electrolyte levels (sodium, potassium and chlorides) is the rule. The mortality rate is from 50 to 75 per cent and the course of disease may be brief. Shock, if lasting longer than two to three hours, is believed to increase the irreversible damage in the tubules. The picture is not so clearcut in all cases; there may not be much fall in blood pressure but hemoconcentration may indicate significant loss of plasma and volume of circulating blood. Vomiting may occur early but may be delayed and appear in terminal uremia. The nonprotein nitrogen invariably rises to high levels. The occurrence of edema is variable. It is usually slight or moderate, sometimes generalized, more often confined to the lower extremities or lungs. Edema of the face is uncommon. Diminution in urinary output may be noted within the first 24 hours. There may be oliguria and generally a highly acid output with low specific gravity which tends to become fixed around 1.010. Smoky urine or frankly bloody urine may be noticed in the first 2 days. In practically all cases there is a positive benzidine reaction due to heme pigment, often transitory and not demonstrable

TABLE 1. *Summary of 35 cases of anuric uremia*

GROUP	CLASSIFICATION (MORPHOLOGICAL BASIS)	DIED	RECOVERY	MORTALITY RATE
	Chronic renal (associated)	18	6	75.0%
1	Acute upper nephron nephrosis (proximal tubules)	8	1	88.8%
2	Acute lower nephron nephrosis (distal tubules)	11	7	61.1%
3	Acute vasospasm (ischemia) (glomerulo-arteriole vasoconstriction)	5	3	62.5%
Average mortality rate		24	11	68.6%

on the third or fourth day. Proteinuria varying in degree persists throughout the illness. Hypertension, an early but moderate rise of the blood pressure, is a fairly consistent finding in urine suppression, believed due to increased production of a pressor substance (renin) by hyperplastic renal tubule cells.

MANAGEMENT

As has been mentioned, the management of the anuric state must be broadly based on the concept that the renal damage is reversible. Although in certain cases this may appear to be an over-optimistic attitude, Thorn[11] has cautioned that the recuperative capacity of the kidney must not be underestimated. The object of treatment is aimed to maintain insofar as possible the normal water balance, acid-base equilibrium, general nutrition, and in case of prolonged renal suppression to provide for the removal of excessive metabolite products and the replacement of certain essential substances which normally are retained by the kidney. To achieve these ends the following measures are advocated:

1. *Early recognition of the oliguric state.* Early recognition of the oliguric state is important. When the urinary output falls below 600 cc per 24 hours, or no urine passes for 12 hours, the question of altered nephron function should arise in the mind of the attending physician. Excessive vomiting in the post-surgical patient and prolonged shock following trauma should arouse suspicion. Abnormal reaction following blood transfusion, abortion, during pregnancy, or occurring in any of the many conditions mentioned under etiology, is cause for diligent attention to the urinary output.

2. *Preservation of blood pressure, blood volume and hemoglobin levels.* Acute, rapidly developing 'kidney failure' as in the 'crush syndrome', post-surgical patient, or following prolonged shock from any cause, is usually initiated by vasospasm of the interlobular arteries or arterioles. This leads to diminished blood flow, cortical ischemia and anoxia, and though unproven in man to activation of the medullary shunt which essentially is a protective mechanism. In management of the initial phase of oliguria the problem, then, is essentially the treatment of shock. The restoration of blood pressure and of circulating blood volume may be accomplished by the transfusion of either whole blood or washed red cells. The release of the neurogenic influence with morphine or intravenous procaine is frequently a valuable adjunct. Determinations of blood urea, sodium, chloride and CO_2 combining power are begun and repeated at least daily to facilitate rational management.

3. *Maintenance of water balance.* When total anuria supervenes, there remain 4 water outlets from the body: lungs, skin, vomitus and feces. The quantity lost by way of the lungs and skin is variously estimated at 600–1000 cc per 24 hours. The excretion by way of the gastro-intestinal tract is measurable. The administration of fluids in quantity sufficient only to replace the fluid loss is considered optimum until the phase of diuresis ensues. Fluids may be given by oral or parenteral routes. In the presence of vomiting, an indwelling gastric tube through which all fluids are given, plus the recovery and return of all vomitus has been

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[11] Thorn, G. W.: Treatment of renal insufficiency. J. Urol., 59: 119, 1948.

found effective in controlling water balance and in replacing electrolyte loss. If possible, the patient should be weighed daily, as fluid loss or gain is more easily determined in this way. During the recovery phase, gradually increasing urinary output should be matched by a corresponding total fluid intake (fig. 1).

4. *Maintenance of electrolyte balance.* In the absence of kidney function, the only other pathways for electrolyte excretion are the stomach and bowel. In the absence of diarrhea and with all vomitus being recovered and returned via a tube there is very little electrolyte loss. Severe acidosis is treated either by oral administration of sodium bicarbonate or by judicious use of intravenous $\frac{1}{6}$ m. sodium lactate solution or Ringer's solution may be used advantageously as it tends to stabilize electrolyte levels. Until the onset of diuresis when chloride is usually excreted in large amounts and should be quantitatively replaced, it is likely that there would be no need for further electrolyte therapy.

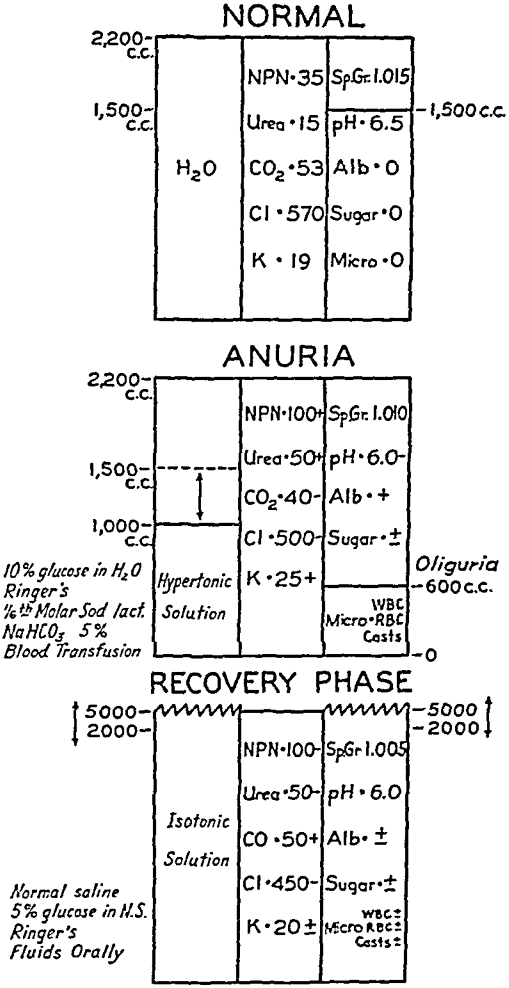

FIG. 1. Showing relationship of fluid intake, blood chemistry and urinary output in oliguric and anuric states.

5. *Rational nutrition.* The two most important factors in nutrition of the anuric patient are a) the highest possible caloric intake, and b) maximum suppression of nitrogenous breakdown. In order to accomplish these ends, a protein-free diet which is high in carbohydrates and fat should be given. Bull, Joekes and Lowe[12] recommend daily intake of the following formula by continuous drip via indwelling gastric tube:

Glucose	400 gm.
Peanut oil	100 gm.
Acacia qs to emulsify	
Water to one liter	
Vitamins optional	

The above mixture furnishes approximately 2500 calories per 24 hours.

6. *Removal of toxic metabolites.* In the milder cases of reversible anuria, while life continues in the absence of renal function, under proper management as outlined above the blood urea increases at an average of 20 to 30 mg. per cent daily. Assuming that one may reasonably expect the onset of diuresis in 5 to 10 days, the nitrogenous retention of itself will not ordinarily prove fatal. In the more severe and prolonged cases, however, the use of supplementary measures such as gastric lavage, intestinal perfusion, peritoneal dialysis or the various types of externally dialyzing 'artificial kidneys' should be considered. The first two are the simplest and probably should be tried first. The latter two are much more elaborate and require the continuous attention of a team of experienced personnel. The external dialyzing machines, while they mark a significant forward step in the treatment of uremia, still require considerable perfection and simplification before they can be said to represent a commonly employed former therapy.

7. *Renal sympathectomy.* The release of neurogenic controls of the vascular pathways of the kidney is advocated by some to counteract cortical ischemia and cellular anoxia. This may be accomplished in a temporary manner through paravertebral or spinal anesthesia and should be tried early in the course anuria if at all. Another method is by unilateral or bilateral renal decapsulation. This procedure accomplishes both the release of sympathetic control and tends to relieve increased intrarenal pressure (a theoretical but unproven concept). Peters,[13] Shapiro[14] and others have reported favorable results in selected cases.

Finally, it should be pointed out that the problem of oliguria and anuria is complex; that all parts of the nephron may be involved simultaneously, that extrarenal factors such as an antidiuretic hormone may be contributory, and that our measures of management still are far from ideal as evidenced by the multiplicity of plans for therapy and diversity of opinion in this regard.

SUMMARY

'Kidney failure' should be classified on the basis of morphological change in the nephron.

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[12] Bull, G. M., Joekes, A. M. and Lowe, K. G.: Conservative treatment of anuric uremia. Lancet, 2: 229, 1949.

[13] Peters, J. T.: Oliguria and anuria due to increased intrarenal pressure. Ann. Int. Med. 23: 221–236, 1945.

[14] Shapiro, I. J.: Renal decapsulation for anuria. J. Urol., 59: 538–543, 1948.

'Anuric' pathogenesis is divided into three phases 1) vasospasm of glomerular arterioles, 2) alterations in function of proximal tubules and 3) mechanical blockage with epithelial destruction in distal tubules.

Principal diseases in which oliguria and/or anuria occurs are listed.

A summary of 35 cases of anuric uremia is presented.

The clinical picture of renal insufficiency is described.

Management is based on the concept that renal damage is reversible and a guide to treatment is outlined under seven headings.

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DISCUSSION

DR. LEON HERMAN (Philadelphia, Pa.): Drs. Farman and Lemon have presented a satisfactory classification of renal parenchymal lesions leading to total dysfunction. I think the classification has the virtue of simplicity without disregard for new facts and theories, but like all classifications, has the inherent fault of oversimplicity, because when the initial lesions of these renal dysfunctions are primarily parenchymal, they soon become exceedingly complex, so that the living pathology is a thing quite apart from the dead pathology.

Eliminating the terminal events in chronic destructive diseases, I am going to speak of the primary parenchymal lesions in which we are primarily concerned. Drs. Farman and Lemon have divided those into three classes: 1) that due to things such as shock, hemorrhage, in which peripheral vascular dysfunction plays a role. These are lesions that are supposed now, in theory, at least, to be due to ischemias, resulting from vasoconstriction, resulting in corticomedullary shunt which it is believed may be maintained to the point where the ischemia results in tubular or epithelial death.

The second group is that in which the renal epithelium suffers in direct ratio to its physiological importance as the result of poisoning, such as that due to heavy metals.

Finally, we have the initial lesion being primarily obstructive as the result of the deposition of deposits from the blood or from ingested chemicals.

We have learned a good deal about these things. We have learned that all these lesions are, at least theoretically, reversible. We have learned, though, that somatic death too often takes place before repair is an accomplished fact. We have learned a good deal about treatment. We have learned to prolong the period in which nature has a chance to exert reversibility. Thus, we have learned not to drown our patients. We have learned to get rid of poisons such as potassium ions and nitrogen ions, particularly by means such as Dr. Kirwin referred to as McCarthy's work and shown by Kelley here in a very fascinating exhibit.

That all of these measures have failed to function to our satisfaction, is indicated by the tremendous mortality which Dr. Farman was forced to report here this morning. It is also exemplified by the prevailing epidemic of artificial kidneys. All of these artificial affairs are the same exactly in physical principle.

I was deeply impressed, when I looked at Dr. Kirwin's and Dr. Lowsley's machine, to see the lack of cumbersomeness and the simplicity of this beautifully executed apparatus, and I know that you gentlemen will join with me in the hope that their hopes for its effectiveness may be completely fulfilled. That it is as yet purely experimental has been acknowledged by Dr. Kirwin and it will take a long time to determine its eventual usefulness. I am absolutely sure that in the very near future somebody is going to walk into the Pennsylvania Hospital and say, "Dr. Herman, if I have to be dialyzed, I want you to use a New York kidney."

DR. GORDON D. OPPENHEIMER (New York, N. Y.): Drs. Lowsley and Kirwin and the American Cystoscope Makers have made a significant contribution to artificial dialysis by the construction of a compact, apparently efficient dialyzer which markets at a price within the reach of most hospitals. However, I believe that it is my duty to make one criticism: We believe that *sterilization* by autoclaving is an essential prerequisite for any so-called artificial kidney which is to be used on patients. The virus of infectious hepatitis, either manifest or latent, can be destroyed, so far as I know, only by steam heat, under pressure. Any part of an artificial kidney which comes in contact with the blood stream of a patient so infected, either latently or manifest, should theoretically be discarded if it cannot be sterilized in that manner.

Their instrument uses the counter-current principle which was embodied in an experimental model exhibited by Rosenak, Saltzman and myself at the 1948 meeting of this association at Boston. Those of you who remember this exhibit from my urological service at the Mt. Sinai Hospital in New York City saw a small, cellophane tubing, "artificial kidney" of new design. Slnce that time, many improvements have been added to increase the safety and efficiency of our *dialyzer. Drs. Rosenak and Saltzman, with the aid of a manufacturing organization*, have carefully chosen the materials used in construction so that the dialyzer, after its assembly, can be sterilized by autoclave.

The wash solution circulates counter-current to the bloodstream for highest efficiency of exchange only once and then is discarded. The blood circuit has been of a vein-to-vein type, a double channel plastic catheter being inserted into the vena cava through any suitable vein. The blood is brought to the dialyzer by a valveless 12-finger pump (previously recorded by Rosenak and Saltzman) and returns to the patient by its own force. A combination of strict aseptic precautions and complete visibility of the dialyzing chambers during use add greatly to the safety of the instrument.

In a recent 2½ hour run on a uremic patient, with the dialyzer setup with an 8,000 sq. cm. area of cellophane tubing, about 100 gm. urea were removed by 50 liters of wash fluid. This figure compares favorably with the output of any extracorporeal dialyzer known to us. Further investigation with this promising method and instrument is in progress on my service. However, I believe it is important at this time to state that this work on dialysis, which started with Abel, Rowntree and Turner in 1912, and which was given such an impetus recently by Kolff, is still highly experimental.

When used to treat a patient with an acute reversible renal insufficiency, it is possible to decrease urea and other diffusible substances and to effect the electrolyte levels in the body fluids and cells by regulation of the levels of these substances in the wash fluid. There are other factors, of course. Unfortunately, our knowledge of uremia is still incomplete, as is our knowledge of the effect of dialysis on the body tissue and economy. Therefore, no urological surgeon should blithely acquire any dialyzer without a careful survey of the historical efforts, the criteria established for its application, the known biochemical changes induced, and the reported and unreported difficulties encountered. Because the method is complicated and time-consuming, competent assistance of a whole group of workers is needed.

Today, a great many patients with acute reversible renal insufficiency are being rescued by careful regulation of their fluid and chemical balance without the use of any form of dialysis. I would venture a guess that probably more patients with acute renal insufficiency have been saved within the last one year solely by reduction of fluid intake to basal requirements than will be saved in the next 5 years by all the methods of extracorporeal dialysis which will be utilized. By that I mean that skillful neglect kills less people than did our previous custom of forcing fluids.

Dr. Walter M. Kearns (Milwaukee, Wis.): Drs. Lowsley and Kirwin have presented an excellent review of the development of various artificial kidneys. It is hoped that their early enthusiasm for their model will be justified when it has been put to more clinical tests.

Our experience has been limited to the clinical use of a modified Kolff kidney. The precepts laid down by Kolff in his pioneer work with the artificial kidney are still our guide in the application of dialysis. The group at the Peter Bent Brigham Hospital at Boston has carried out careful investigative work and applied dialysis to over one hundred patients using the Kolff kidney. Their success led us to adopt the Kolff type of kidney.

Table 1. *Selective dialysing artificial kidney**

Patient: J. B.

	N.P.N.	CREATININE	CHLORIDES
Blood before dialysis	149 mg.	14.4	562 mg.
Blood leaving artificial kidney	49 mg.	6.4	603 mg.

* Tests made during first one-half hour.

It was our good fortune at Columbia Hospital in Milwaukee to have the benevolence and cooperation of a large industrial concern, whose chief physicist, our guest here today, Mr. Wilson, has deftly used the many facilities of their research department. A number of improvements have resulted in a most practical artificial kidney.

Table 1 records the effectiveness of dialysis in clearing nitrogenous waste products from the blood, correcting acidosis, and conserving essential electrolytes. Under all of the headings, the column on the left gives the concentration in the venous blood of the patient. The columns on the right show the concentration as blood leaves the artificial kidney. The effectiveness of the artificial kidney in removing the nitrogenous waste products is quite apparent in the marked reduction in the concentration of nonprotein nitrogen and creatinine in the blood leaving the apparatus, as well as the improvement in the patient's blood at the end of the 5 hour period. Under the third heading, the figures indicate that the concentration of chlorides in the blood was conserved. In the fourth column a gradual correction of the acidosis is revealed. In the third hour, when the usual concentration of sodium bicarbonate in the replenished bath was doubled, a very marked clinical improvement, in the rapid, deep, acidotic type of hyperventilation occurred. The increase in the CO_2 combining power of the blood confirmed the observed return to normal respiration.

The necessity of ruling out the presence of obstruction in the urinary tract is well impressed in another patient (table 2) in whom generalized urticaria and edema with marked edema of the bladder caused obstruction to both lower ureters. It was impossible to visualize either ureteral orifice at the first cystoscopy. In the application of the artificial kidney, the bath was made hypertonic with added glucose in order to reduce the edema. Cystoscopy was repeated the following morning, and the orifices were visualized and catheterized. Ureteral *drainage approximated 6000 cc per 24 hours during the ensuing days, followed* by the *patient's recovery*.

Our group believes that artificial dialysis is a safe procedure which effectively removes nitrogenous waste products from the blood. It should not be a substitute, however, for the careful medical management of acute anuria. We have no convincing evidence that the removal of nitrogenous waste products alone has been life saving. We are disturbed by the fact that patients admitted have been water logged by the excessive administration of salt and fluids and are suffering from edema, congestive heart failure, and hypertensive encephalopathy. At this moment, we believe that artificial dailysis has been life saving in correcting these complications by removing this excessive salt and water from the extracellular space.

Table 2. *Comparative chemical determinations**

Patient: W. B. Acute Hemolytic Episode of Unknown Cause; Bilirubin 26 mg.%

TIME	BLOOD				PLASMA			
	NPN Mg. %		Creatinine Mg. %		Chlorides MEq/L		CO_2 Vols. %	
	Before	After	Before	After	Before	After	Before	After
Hours								
1	340	113	28.5	17.5	85	92	22	27
2	315	78	27	8.0	89	96	22	27
3	280	120	21.5	17.5	85	92	25	45*
4	290	38	25	15.0	92	96	27	36
5	280	78	19	6.5	89	96	27	56

* Additional $NaHCO_3$ to bath because of clinical acidosis.

A permanent team composed of men in several specialties including urologist, surgeon, internist, chemist and several trained residents is necessary. There is no better example of the interdependence of the various specialties and the need for their cooperative action than in the application of the artificial kidney.

Dr. J. Hartwell Harrison (Boston, Mass.): The problem of external dialysis has been studied by Drs. Thorn, Merrill, Walter and associates during the past 2 years at the Peter Bent Brigham Hospital. The work has gone forward as a problem which is yet in a state of clinical investigation and represents a cooperative team effort. I think it is important to emphasize that the role of the urologist is fundamental in the selection and preparation of patients for treatment by this method as well as in their aftercare.

It is quite significant that Drs. Lowsley, Kirwin, Slotkin and other urologists have contributed to the simplification of the mechanical aspects of external dialysis in addition to their other contributions to this work. We have all profited from the work and cooperation of Dr. Oppenheimer.

I should like briefly to outline some of the deductions that have been drawn as the result of this experience during the last two years by Thorn and his associates: 1) It is possible and feasible to remove diffusible substances from the circulating blood such as sodium, potassium, calcium, water and a vasodepressor substance probably produced in the diseased liver. 2) This procedure can be carried out without hazard to the patient. 3) The treatment can be repeated if necessary. 4) When external dialysis is indicated it should not be postponed as a last resort when it is available. 5) In addition to nitrogen metabolites, other diffusible substances can be removed, such as barbiturates and sulfonamides. I would like to emphasize that patients becoming anuric following transurethral prostatectomy as a result of hemolysis in our experience should not have external dialysis postponed for ten days to two weeks as a last resort. It has not been shown that hemolysis is due entirely to the use of distilled water and that there are no other factors concerned. However, we do not need to use distilled water and I believe from our experience that it should not be used any longer in the operation of transurethral prostatectomy. There is another aspect of this which has not been emphasized, namely, that with certain types of transurethral prostatectomy there is a rather significant degree of internal burn. This varies in area and depth as well as degree in different patients and may be a factor in contributing also to hemolysis.

The urologic conditions which you might be interested in that have been treated selectively are: Severe renal failure following long-standing hyperplasia of the prostate with urinary retention. In such cases this is not a life-saving procedure, but from time to time it permits one to prepare the patient for operation more quickly than could be accomplished otherwise. This has been employed in only one or two instances by us. Similarly, patients with stricture of the urethra having chronic renal insufficiency have had their hospital course shortened significantly by external dialysis. It has been of value in the management of the diabetic patient with necrotizing pyelonephritis and renal insufficiency both before and after surgery. It has been useful as a safeguard for patients having bilateral nephrolithiasis and chronic pyelonephritis. It has offered us a security in such patients with bilateral staghorn calculi whom we would have otherwise been hesitant to operate upon for fear of postoperative anuria. Such patients having renal insufficiency may be prepared more quickly for surgery by external dialysis.

DR. GEORGE E. SLOTKIN (Buffalo, N. Y.): I simply want to show the machine that we have used. It is simple and does not require, as other machines do, a large team of doctors to manipulate it. The only factor, I believe, and the difference between our machine and the other machines—and they are all valuable; don't misunderstand me—is the fact that we employ the largest pool of blood with which we can come in contact in the human body, namely, we catheterize or cannalize the vena cava. We do so by dissecting down on the saphena magna which is easily found in the groin employing the largest polyethylene catheters

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By this means, we believe that we do not put any tax on the heart, so that the patient to whom this kidney is applied is not subjected to any unusual cardiac burden, nor is any extra reserve required so far as his heart is concerned.

(Slide) Ours is a simple machine which uses a simple gasoline fuel pump that is kept in operation by a $\frac{1}{6}$ h.p. motor. The blood, efferent from the vena cava, enters the pump, is kept in circulation, enters the lower portion of the dialyzing membrane (100 feet of viscose sausage casing), comes in contact with the dialyzing fluid. We use the modified Tyrode solution which we believe is the best. It is kept at normal temperature by a thermostat, which I will show you in the other slide, and kept in circulation by a small propeller inside.

The afferent to the patient then goes to the other catheter, which also enters the vena cava.

(Slide) This shows you one other view of the machine. As far as sterilization is concerned, this machine is easily sterilized. We have run innumerable experiments on infection. Here is your pump, which is plastic with a rubber cap which is sterilized by 1-1000 zephiran solution for 2 hours while the patient is being prepared. The only other point of circulation is the viscose tubing which is autoclaved. The rest is regular transfusing tubing.

This kidney of ours has been applied to a four-year-old child and in older people. We have no quarrel with any other kidney but we believe that simplicity is very important. The only part that the urologist plays in this factor is the canalization of the vena cava, and then the future operation of the kidney can be carried on by a couple of trained nurses, with the laboratory to determine the constituents of the blood and the amount of urea which is extracted.

In the last case, which was in Baltimore, Dr. Goldstein's case, the kidney reduced the urea within 8 hours to *normal*. The patient had swallowed some cyanide of mercury.

I think the important thing in any of these kidneys is that every possible means should be exhausted to allow the kidney to regenerate. We differ from the people at Peter Bent Brigham Hospital; we employ everything possible we know of and do not apply this kidney except in moribund cases.

Finally, we are all looking for the same result. Our destination is the same, to dialyze the blood and wash out all the nitrogenous products.

Dr. Budd C. Corbus, Jr. (Fargo, N. Dak.): Mechanical dialysis by the Kolff kidney or its modification, in an area remote from a metropolitan or university hospital medical center, is well nigh impossible and rather impractical. The use of transperitoneal dialysis has been considered by many as a formidable and dangerous procedure. I have had a very brief experience, which is not enough to deduce any conclusions but enough to convince me that the procedure is simple, nondangerous, and not hazardous to the life of an individual that is already jeopardized by a possible fatal uremia.

When we know that uremia is going to be fatal, the medical men insist you must try everything conservative possible. Many urologists, on the other hand, say that you must take only those people who are virtually terminal. Dr. Harrison's internal burn, I believe, corresponds to the pathologist's conception of tubular destruction below the basal membrane. If it does occur below the basal membrane, we know that tubular regeneration will not occur and the uremia is irreversibly progressive. If the tubular destruction is not below the basal membrane, with conservative measures, the majority will recover.

How do we know that clinically? I believe that it is impossible to diagnose tubular obstruction clinically. Therefore, I believe that the institution of a simple procedure, such as we have in transperitoneal dialysis, is justifiable in those cases which we think may come to termination. The procedure does not employ the complicated tubes, such as the polyethylene tubes which have been utilized by some, but merely a 30 F mushroom catheter, which is inserted in the right and left quadrant through a Bergmann incision. The dialyzing solution is a hypertonic electrolyte, such as Hartman's solution which includes 20 mg. of heparin and 300,000 units of penicillin.

This dialysis is continued for 4 days and then completed. At that time, these tubes are removed, antibiotics are instilled into the peritoneal cavity, and peritonitis is completely avoided.

Dr. Franklin Farman (Whittier, Calif.): I should like to emphasize one or two points: First, a diet absolutely free from protein is necessary, but one rich in carbohydrate and fat in order to maintain proper nutrition of the anuric patient and to prevent further nitrogenous breakdown. Another point I wish to mention is the question of renal sympathectomy. There are many reported cases, and one of our own, in which the patients have recovered following unilateral or bilateral renal decapsulation. This procedure accomplishes both the release of sympathetic control and tends to relieve increased renal pressure (a theoretical but unproven concept) and in reported cases by Drs. Peters, Shapiro and others, recovery has followed in selected instances.

Dr. Thomas J. Kirwin (New York, N. Y.): I first wish to thank Dr. Herman for his discussion and to congratulate Dr. Kearns for his excellent results. Let me relieve Dr. Oppenheimer's mind as to the steam sterilization. We sterilize abdominal skin with an antiseptic solution before the incision is made and we do not have to steam them. We use a 1/1000 urolocide solution, accepted by the United States Government, which is even more potent than some others that are still used. It kills the deadliest Staphalococcus aureus for us far sooner than the Government requires. Our tanks are not only sterilized with it, but our dialyzing chambers and all apparatus that is used are kept in this solution as long as 3 or 4 hours and sometimes overnight. After repeated bacteriological examinations we have been unable to recover any bacteria.

I am well acquainted with the work of Dr. Thorn and his co-workers in Boston. It is excellent. I particularly like the simplicity of Mr. Wallace's machine which does not require five or six men; you need only 2; in fact, one with a nurse. It is impossible to go wrong. The blood is taken from the patient on one side, through the dialyzer, and put back in on the other side. If it could be simpler than that, I do not know how you would do it.

I should like to remind urologists that the gynecologists have taken over much of the work on sterility with which the urologists formerly had a great deal to do. They have also taken over practically all the renal surgery of women—in fact, all the female genito-urinary surgery. General surgeons throughout the country are practicing a great deal of urology. The dermatologists are treating lues. In anuria, however, most of the work along this line has been done by urologists. I at least think we are capable enough of knowing the normal physiology of the kidney and of reviewing the work which Dr. Richards of Philadelphia has done at the University of Pennsylvania as well as that which Dr. Homer Smith of New York has done at the New York University. I believe that we ought to get on the band wagon and keep anuria for the urologists.

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TRANSTHORACIC NEPHRECTOMY (LEFT) FOR WILMS' TUMOR

VINCENT J. O'CONOR AND JEROME R. HEAD

From the Department of Urology, Northwestern University Medical School, Wesley Memorial Hospital, Chicago

In 1948, we reported at a meeting of the North Central Section a successful and satisfactory transthoracic (retroperitoneal) right nephrectomy for tuberculosis. The patient had such an extreme kyphosis that neither a lumbar nor an abdominal approach to the kidney was possible.

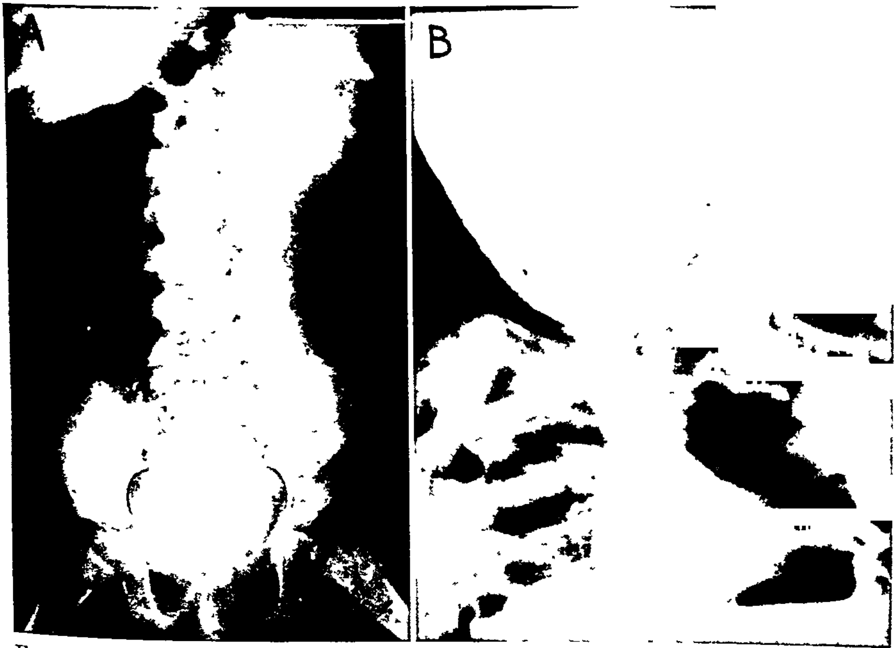

FIG. 1. *A*, plain film, May 19, 1949, shows soft tissue outline of left abdominal mass. Excellent reduction of previous dislocation of left hip. *B*, chest film, May 19, 1949, reveals lung fields to be clear. Left leaf of diaphragm is slightly elevated secondary to large tumor mass occupying left side of abdomen.

A recent experience has again demonstrated the utility of the transdiaphragmatic approach in a selected case.

A 2 year old girl had been under treatment at Wesley Memorial Hospital for a dislocated hip which necessitated the wearing of a body cast for 4 months. Upon the removal of the cast it was noticed that the left abdomen was almost completely filled by a palpable tumor mass. This enlargement seemed to be definitely retroperitoneal and after an excretory urographic study a diagnosis of tumor of the left kidney (Wilms') was made (figs. 1 and 2). X-ray therapy was instituted and during the period from May 23 to June 9, 1949 the patient received 14 treatments to three left abdominal ports for a total of 2400 r. measured in air. This is equivalent to a total skin dose of 3326 r. Estimated tumor dose

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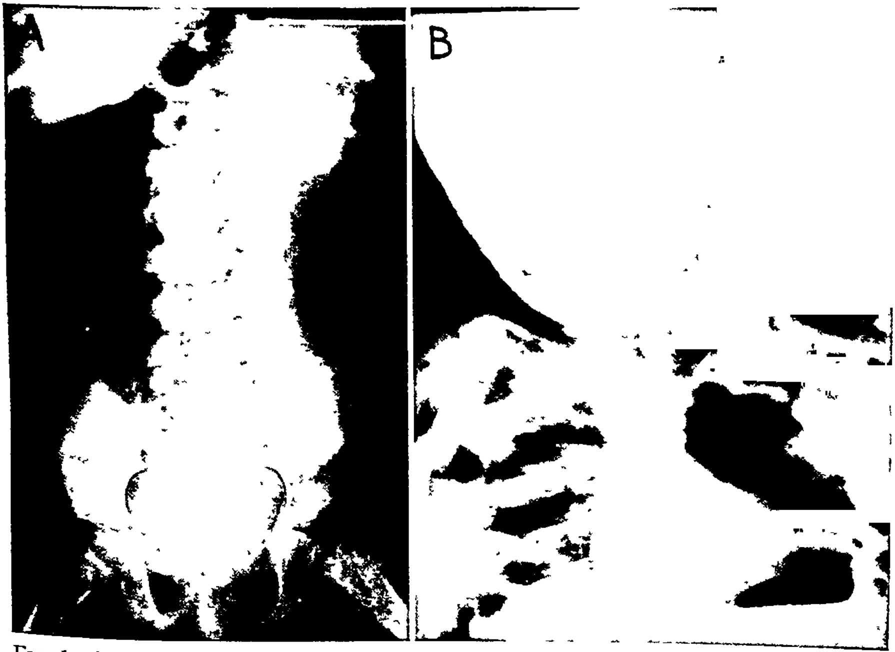

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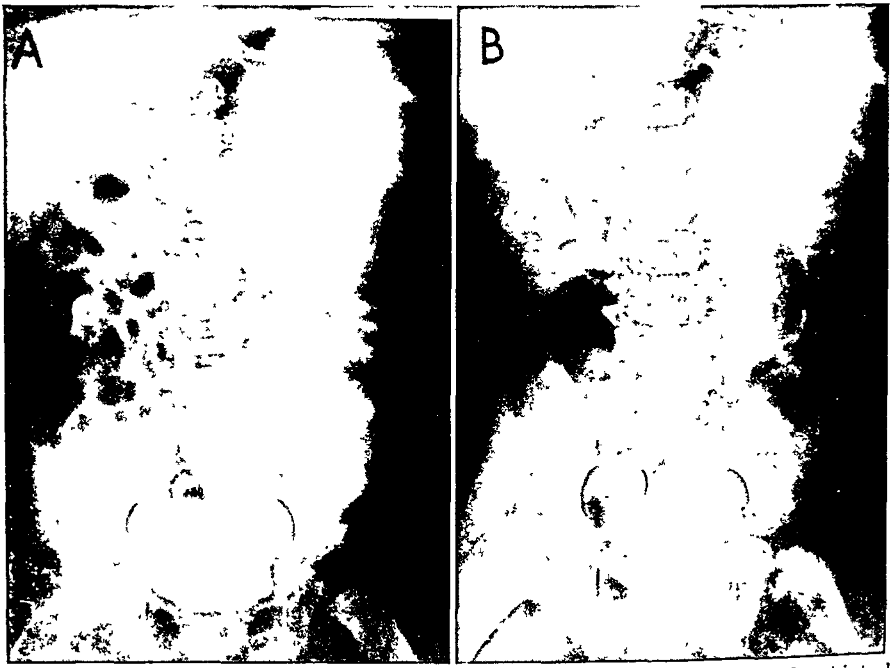

FIG. 2. *A*, excretory urogram, May 23, 1949, shows large tumor mass on left which displaces and distorts calyceal system of left kidney. Diagnosis: Wilms' tumor, left kidney. *B*, excretory urogram, June 10, 1949, shows marked regression in size of left renal tumor but with tumor mass very high in left loin and extending upward to ninth rib.

The patient's preoperative condition was good although the hemoglobin was 9.5 gm. (61 per cent) with 3,360,000 red blood cells and 14,250 white blood cells.

On June 16, under satisfactory inhalation anesthesia, an incision paralleling the entire left eleventh rib was made. The rib was removed subperiosteally in the usual manner. The chest wall was opened, the lung was retracted and the diaphragm incised carrying the muscle separation as far posteriorly as possible. In this manner we immediately exposed a large left renal tumor without opening the peritoneum. The renal pedicle was visually accessible and the kidney (fig. 3)

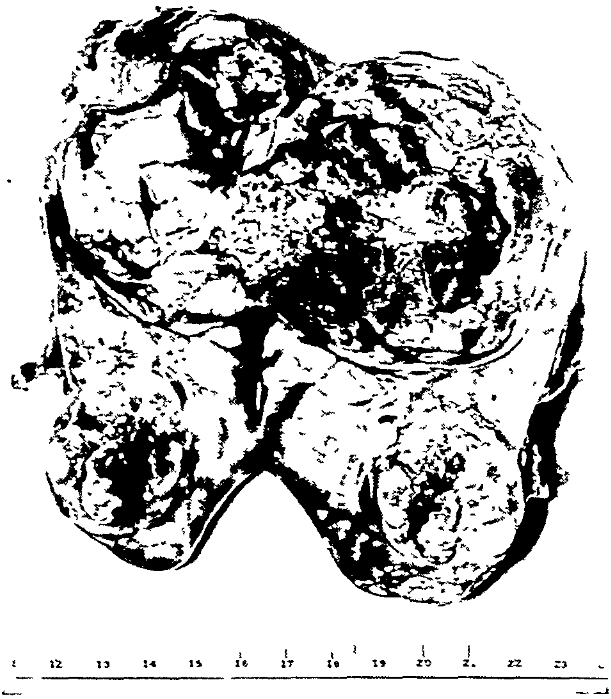

FIG 3. Left kidney removed June 16, 1949 through left transthoracic retroperitoneal approach. Diagnosis: Wilms' tumor of left kidney.

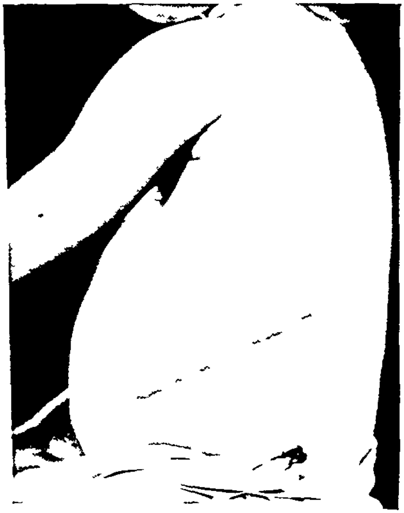

FIG 4 October 1, 1949, photograph of patient shows location and extent of incision for left transthoracic nephrectomy.

was removed with great ease. One lymph node at the hilus of the kidney was removed. The field was completely dry and the diaphragm was closed with interrupted chromic sutures. An 18F mushroom catheter was placed in the pleural cavity and brought out the posterior angle of the incision. The patient left the table in good condition.

Convalescence was uneventful, the wound healed nicely per primam after removal of the chest catheter in 48 hours. Pathological report: Nephroblastoma or mixed tumor of left kidney. The patient was sent home on the fourteenth postoperative day.

Three months later the child's general health was good and she had gained 6 pounds in weight. A chest film on September 24, 1949 showed normal findings except for slight elevation of the diaphragm on the left.

The location and extent of the incision are shown in figure 4.

SUMMARY

A left, transthoracic, retroperitoneal nephrectomy on a 2 year old girl for the removal of a Wilms' tumor is reported. Because of the high position of the kidney it is believed that the ease of operative performance was made possible by the transdiaphragmatic approach.

55 E. Washington St., Chicago, Ill.

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SERUM ALBUMIN IN UREMIA: A CLINICAL INVESTIGATION CORRELATED WITH REVERSIBLE UREMIA IN DOGS

ROGER BAKER

From the Department of Surgery, the University of Chicago, Chicago

Gross and microscopic changes are often only the advanced manifestations of disease. The pathological physiology involved is the earlier cause of most morphological abnormalities. Though much has been learned concerning the abnormal physiology of uremia, the most obvious and basic questions remain unanswered. Fundamental information is essential to eventual understanding of the obscure *modus operandi* of this vital disease state.

The objectives of this study were three: to develop a practical experimental method for producing reversible uremia; secondly to apply the procedure to experimental animals for study of serum proteins in uremia; and finally to carry the protein investigation from the laboratory to the patient in uremia.

Diverse methods exist for the production of experimental uremia. Prominent are partial nephrectomy,[1-3] bilateral nephrectomy,[4-8] compression of renal pedicle,[9, 10] temporary, complete compression of renal artery,[11, 12] permanent incomplete occlusion of renal artery,[13] ligation of ureters,[14, 15] anastomosis of ureters

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Read at annual meeting, American Urological Association, Washington, D. C., May 31, 1950.

This investigation was supported in part by the Douglas Smith Foundation.

Dr. Baker's paper was awarded a prize by The Committee on Scientific Research, American Urological Association, Dr. Miley B. Wesson, chairman. *Editor*

[1] Chanutin, A. and Ferris, E. B., Jr.: Experimental insufficiency produced by partial nephrectomy. Control Diet. Arch. Int. Med., **49:** 767–787, 1932.

[2] Tuffier, T.: Etudes experimentalles sur la chirurgie du reins. Paris, G. Steinheil, 1889; quoted by Pearce, R. M., J. Exper. Med., **10:** 632, 1908.

[3] Hartwich, A.: Der Blutdruck bei experimenteller Uramie und partieller Nierenausscheidung. Ztschr. f. d. ges. exp. Med., **69:** 462, 1929.

[4] Herter, C. A.: The results of experimental nephrectomy in dogs as bearing upon the uraemic state. M. Rec., **52:** 280, 1897.

[5] Mikuriya, I.: Experimental uremia. Hukuoka acta med., **33:** 5–6, 1940.

[6] White, B. H. and Harkins, H. M.: Treatment of experimental uremia by intestinal lavage. J. Lab. & Clin. Med., **32:** 1434, 1947.

[7] Fuentes, Varelas B., Duomarco, J. and Munilla, A.: Experimental uremia induced in dog by bilateral ureteral ligature and double nephrectomy; distribution of total NPN in blood. Rev. Asoc. Med. Argent., **42:** 423–430, 1929.

[8] Huggins, C. and Sibly, J.: Effect of parabiosis on experimental uremia. Proc. Soc. Exper. Biol. & Med., **63:** 85–87, 1946.

[9] Allen, F. M.: Experimental production of various renal vascular disorders. J. Urol., **49:** 512, 1943.

[10] Mason, M. F., Resnik, H., Minot, A. S., Rainey, J., Pilcher, C. and Harrison, T. R.: Mechanism of experimental uremia. Arch. Int. Med., **60:** 312–336, 1937.

[11] Hamilton, P. B., Phillips, R. A. and Hiller, A.: Duration of renal ischemia required to produce uremia. Am. J. Physiol., **152:** 517–522, 1948.

[12] Badenock, A. W. and Darmady, E. M.: Temporary occlusion of renal artery in rabbits. J. Path. and Bact., **59:** 79–94, 1947.

[13] Drury, D. R.: Production of renal insufficiency by surgical procedure. Proc. Soc. Exper. Biol., **29:** 856–857, 1932.

[14] Atchley, D. W. and Benedict, E. M.: Distribution of electrolytes in dogs following ligation of both ureters. J. Biol. Chem., **73:** 1–14, 1927.

[15] Condrodt, J.: Production of uremia in dogs by anuria due to low ligation of ureters. Rev. belge sc. med., **11:** 41–84, 1939.

to different levels of small intestine,[16, 17] ureterovenous anastomosis,[18-21] and x-ray radiation of kidneys.[22] Heavy metal injection,[23] intravenous toxins,[24, 25] and crush injury[26] may also be mentioned. Intrinsic in these methods are certain obvious defects for the experimental study of serum proteins. The majority of procedures introduce variables which would confuse results observed; e.g., the unknown effect on serum proteins of a liver damaged while either radiating the kidneys or administering heavy metals intravenously for the production of uremia.

No method was found in the literature which permitted the selection of a specific degree of uremia or could be terminated so as to completely restore the uremic animal to the pre-uremic, normal condition. These exacting demands of a technique were required so data obtained during the experiment could be assumed significant of the uremic state per se and uninfluenced by the method used to produce the uremia. A benign procedure which tends to avoid these defects was devised in the present experiments.

Investigation of serum albumin involves qualitative as well as quantitative determinations. The measurement of albumin concentration by weight per 100 cc of plasma is well known and universally employed. Measurement of alterations in the quality or kind of albumin is known but seldom used clinically. In essence this depends on the phenomenon that certain molecules have an affinity for serum proteins. There is attraction between the negative charged molecule (anion) and the serum protein which acts as a positive charged (cationic) center. This affinity results in a binding of the molecule to the protein. The amount adsorbed by the protein may be measured. Departure from the normal measurement indicates abnormal protein.

These findings have more than abstract interest when applied to the human organism. In 1923, Marshall and Vickers[27] observed during a study of the mech-

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[16] Baird, J., Scott, R. and Spencer, R.: Studies on the transplantation of the ureters into intestine. Surg., Gynec. & Obst., **24:** 482, 1917.

[17] Bollman, J. L. and Mann, F. C.: Nitrogenous constituents of blood following transplantation of ureters into different levels of intestine. Proc. Soc. Exper. Med., **24:** 923, 1927.

[18] Hartwich, A.: Experimental uremia. Transplanting ureters in vein. Verhandl. d. deutsch. Gesellisch. f. inn. Med. Kong., **40:** 303–307, 1928.

[19] Serra, G.: L'anastomosi uretero-venora e le sue conseguenze specialemente in rapporto con la genesi dell' uremia. Arch. ital. di. Chir., **22:** 137, 1928.

[20] Dragstedt, L. R. and Greer, W. A.: Studies on renal hypertension. Ann. Surg., **108:** 263–270, 1938.

[21] Lozzi, V.: Production of uremia by ureterovenous anastomosis; experiments on dogs. Policlinics (sez chir), **39:** 229–252, 1932.

[22] Hartman, F., Bolliger, A. and Doub, H.: Functional studies throughout the course of roentgen-ray nephritis in dogs. J.A.M.A., **88:** 139, 1927.

[23] Hoff, H. E., Smith, P. K. and Winkler, A. W.: Cause of death in experimental anuria. J. Clin. Invest., **20:** 607, 1941.

[24] Aliev, A.: Biochemical change of the blood in experimental nephritis. Klin. Med., **18:** 40–44, 1940.

[25] Owada, K.: Experimental studies on changes in the proteins, carbohydrates and gases in preserved blood. II. Cholemic and uremic blood. Tohoku J. Exptl. Med., **38:** 262–292, 1940.

[26] Andrews, E.: Experimental uremia. Arch. Int. Med., **40:** 548, 1927.

[27] Marshall, E. K., Jr. and Vickers, J. L.: Mechanism of the elimination of phenolsulphonephthalein by the kidney—A proof of secretion by the convoluted tubules. Bull. Johns Hopkins Hosp., **34:** 1–7, 1923.

anism of elimination of phenolsulfonephthalein (PSP) by the kidney that all the PSP injected intravenously did not exist in a free state in the plasma. The possibility was presented that the PSP was bound to colloids. De Haan[28] published data proving that dyes of this type were bound to the plasma to some extent. Grollman[29] proved that PSP was bound to serum albumin.

Aschoff discovered the reticulo-endothelial system by dye-globulin binding.[30] Oxygen is transported throughout the circulatory system bound to the protein hemoglobin. Iodine,[31] bile salts,[30] and the estrogen, estriol,[32] are also bound to serum protein. Uric acid exists partly free, partly bound. Therapeutically important, sulfonamides are bound to serum albumin and are thus carried through the body.[33] Those sulfonamides with the greatest binding properties are the greatest antibacterial agents. Penicillin bound by albumin has definite antibacterial activity.[34]

Grollman[29, 36] and others[37-40] have analyzed protein binding with important conclusions: The dye PSP is adsorbed to serum albumin. The amount adsorbed is dependent on the quality of the albumin. It is highly significant from a clinical investigative viewpoint that at the pH of blood this binding is due primarily to serum albumin and not globulin. Further, the adsorption follows certain definite physical chemical laws which prove that the quantity of albumin bound is proportional to alterations in concentration of albumin. This permits the establishment of a quantitative basis for measurement of the amount of dye bound.

In disease significant fine abnormalities of the albumin molecule may be observed by application of these principles. Bennhold[30] discovered impaired binding in amyloidosis and cirrhosis. Gottlieb[41] and Bennhold[30] noted abnormally low binding of dye in certain cases of nephrosis. A paucity of data exists relative to qualitative protein alterations in uremia. Onishi[42] and Bennhold[30] in the course of other investigations comment on a decrease or tendency toward decrease in dye-binding in renal insufficiency. The present paper utilized the binding of PSP to study serum albumin in uremia.

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[28] de Haan, J.: The renal function as judged by the excretion of vital dye stuffs. J. Physiol., **56**: 444, 1922.

[29] Grollman, A.: The combination of phenol red and proteins. J. Biol. Chem., **64**: 141–160, 1925.

[30] Bennhold, H.: Uber die Vehikel funktion der Serumeiweisskorper. Ergeng. Innere Med. Kinderheilkun., **42**: 273–375, 1932.

[31] Bassett, A. M., Co, A. H. and Salter, W. T.: Protein bound iodine in blood. Am. J. Med. Sc., **202**: 516, 1941.

[32] Boettiger, E. G.: The adsorption of estriol by the plasma proteins. J. Cell. Comp. Physiol., **28**: 139, 1946.

[33] Davis, B. D. and Wood, W. B., Jr.: Studies on antibacterial action of sulfonamide drugs. III. Correlation of drug activity with binding to plasma proteins. Proc. Soc. Exper. Biol., **51**: 283, 1942.

[34] Chow, B. F. and McKee, C. M.: Interaction between crystalline penicillin and human plasma proteins. Science, **101**: 67, 1945.

[35] Coolidge, T. B.: Chemistry of the Van Den Bergh reaction. J. Biol. Chem., **123**: 119, 1940.

[36] Grollman, A.: The relation of the filterability of dyes to their excretion and behavior in the animal body. Am. J. Physiol., **75**: 287–293, 1925.

[37] Robinson, H. W. and Hogden, C. G.: The influence of serum proteins on the spectrophotometric absorption curve of phenol red in a phosphate buffer mixture. J. Biol. Chem., **137**: 239, 1941.

[38] Bennhold, H., Kylin, E. and Ruszynak, S.: Die Eiweisskorper des Blutplasmas. Dresden: T. Steinkopff, 1938.

[39] Klotz, I. M. and Urquhart, J. M.: Bending of organic ions by proteins. Comparison of native and modified proteins. J. Am. Chem. Soc., **71**: 1597–1603, 1949.

[40] Klotz, I. M. and Walker, F. M.: The binding of organic ions by proteins. Charge and pH effects. J. Am. Chem. Soc., **69**: 1609–1612, 1947.

METHODS

I. Production of reversible uremia. Required material consists of one 15 cm. length of 0.6 cm. diameter Penrose rubber drain.

Healthy adult male and female mongrel dogs were selected, and all operations were performed under ether anesthesia while observing usual aseptic precautions. Either a right or left rectus muscle-splitting incision was made. The distended bladder was emptied by pressure on the fundus. Slight tension on the dome of the bladder immediately identified the ureters as tube-like structures tenting up the posterior parietal peritoneum. Approximately 2.5 cm. from the vesical junction the ureters were carefully freed from their beds. No attempt was made to strip ureters of adventitial tissues. Preservation of ureteral vascular supply was rigidly maintained. A length of empty Penrose drain was passed beneath the ureters (fig. 1) and the ends brought through a separate stab-wound in the midline (in the male superior to the base of penile skin). Trial tension on the ends of the rubber drain must produce equal tension of ureters. The ureters were then returned to their original anatomical location and the ends of the relaxed rubber drain sutured to the skin. The primary incision was closed in the usual manner.

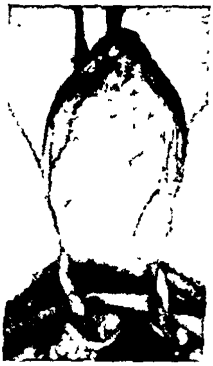

FIG. 1. Posterior surface of dog's bladder demonstrating Penrose rubber drain beneath isolated ureters.

When desired, uremia was induced by increasing tension on the drain. The degree of tension applied determined the amount of ureteral occlusion and hence the degree of uremia. Simple suture of the drain to the skin maintained tension without pain to the animal. Cutting the restraining suture terminated uremia. The angulation of the ureters thus released permitted the ureters to drop to their normal course. They were aided in this direction by pressure from the bladder distending with urine and producing pressure anteriorly on the ureters which were angulated near the base of the viscus.

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[41] Gottlieb, H. and Ludwig, H.: Uber adsorption von Farbstaff aus Serum an Kohle. Z. Klin. Med., **131:** 358, 1936.

[42] Onishi, Y. and Suga, M.: Ueber die Adsorptions fahigkeit des Blutserums gegenuber saurem Farbstaff bei Weilscher Krankheit sowie verschiedenen *Lebererkrankungen*. Mitt. a. d. Med. Akad. Zu Kioto, **28:** 287, 1940.

II. Qualitative protein analysis. The method of Huggins et al.[43] was used for determination of PSP binding by equilibrium dialysis. One hundred mg. phenolsulfonephthalein was dissolved in 100 cc of M/15 phosphate buffer, pH 7.4. A 15 cm. length of cellulose casing (diameter 1.75 cm.) was knotted at one end. One cubic centimeter of the above PSP stock solution and 1 cc of serum were placed in the bag and the other end knotted. The bag was immersed in a flask containing 98 cc of distilled water and attached to a rotator at 5 C for 48 hours. Equilibrium was reached in 40 hours between protein solution and dialysate. After warming to room temperature 10 cc of dialysate was diluted with water, 1 cc of 5 N NaOH added, and the volume brought to 100 cc with water. Readings were made using the Evelyn Photoelectric Colorimeter with 540 $m\mu$ filter. The colorimeter reading indicates the PSP not bound by protein within the cellulose bag. Subtraction of this figure from the standard reading of PSP yields the amount of dye bound to albumin.

The quantity of circulating serum albumin varies from day to day, from patient to patient, and from normal to disease. Consequently, as there is a variable quantity of albumin in each cubic centimeter of serum used, significant binding results are necessarily expressed as a ratio or index relating the bound PSP to weight of albumin per 100 cc. The calculation is:

$$\text{Binding Index} = \frac{\mu\text{gm of PSP bound}}{\text{Albumin Gm./100 cc.}}$$

III. Quantitative protein analysis. Albumin was determined by Howe[44] fractionation as modified by Weichselbaum[45] and nitrogen content according to the micro-Kjeldahl method of Ma and Zuazaga.[46] Correction was made for nonprotein nitrogen.

IV. Nonprotein nitrogen analysis. Determinations were made by the routine method of Folin and Wu[47] as modified by Koch and McMeekin.[48] Determinations of nonprotein nitrogen and PSP-binding were performed in duplicate.

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[43] Huggins, C., Jensen, E. V., Player, M. A. and Hospelhorn, V. D.: The binding of phenolsulfonephthalein by serum and by albumin isolated from serum in cancer. Cancer Research, 9: 753, 1949.

[44] Howe, P. E.: The use of sodium sulfate as the globulin precipitant in the determination of proteins in the blood. J. Biol. Chem., 49: 93–107, 1921.

[45] Weichselbaum, T. E.: An accurate and rapid method for the determination of protein in small amounts of blood serum and plasma. Am. J. Clin. Path., 7: 40–49, 1946.

[46] Ma, T. S. and Zuazaga, G.: Micro-Kjeldahl determination of nitrogen. A new indicator and an improved rapid method. Industrial and Engineering Chemistry (Analytical Edition), 14: 280, 1942.

[47] Folin, O. and Wu, H.: System of blood analysis. J. Biol. Chem., 38: 81, 1919.

[48] Koch, F. C. and McMeekin, T. L.: A new direct nesslerization micro Kjeldahl method and a modification of the Nessler-Folin reagent for ammonia. J. Am. Chem. Soc., 46: 2066, 1924.

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METHODS

I. Production of reversible uremia. Required material consists of one 15 cm. length of 0.6 cm. diameter Penrose rubber drain.

Healthy adult male and female mongrel dogs were selected, and all operations were performed under ether anesthesia while observing usual aseptic precautions. Either a right or left rectus muscle-splitting incision was made. The distended bladder was emptied by pressure on the fundus. Slight tension on the dome of the bladder immediately identified the ureters as tube-like structures tenting up the posterior parietal peritoneum. Approximately 2.5 cm. from the vesical junction the ureters were carefully freed from their beds. No attempt was made to strip ureters of adventitial tissues. Preservation of ureteral vascular supply was rigidly maintained. A length of empty Penrose drain was passed beneath the ureters (fig. 1) and the ends brought through a separate stab-wound in the midline (in the male superior to the base of penile skin). Trial tension on the ends of the rubber drain must produce equal tension of ureters. The ureters were then returned to their original anatomical location and the ends of the relaxed rubber drain sutured to the skin. The primary incision was closed in the usual manner.

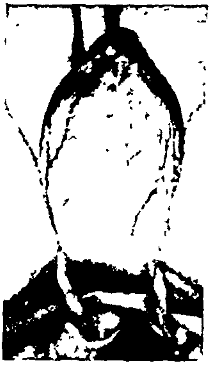

FIG. 1. Posterior surface of dog's bladder demonstrating Penrose rubber drain beneath isolated ureters.

When desired, uremia was induced by increasing tension on the drain. The degree of tension applied determined the amount of ureteral occlusion and hence the degree of uremia. Simple suture of the drain to the skin maintained tension without pain to the animal. Cutting the restraining suture terminated uremia. The angulation of the ureters thus released permitted the ureters to drop to their normal course. They were aided in this direction by pressure from the bladder distending with urine and producing pressure anteriorly on the ureters which were angulated near the base of the viscus.

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[41] Gottlieb, H. and Ludwig, H.: Uber adsorption von Farbstaff aus Serum an Kohle. Z. Klin. Med., **131:** 358, 1936.

[42] Onishi, Y. and Suga, M.: Ueber die Adsorptions fahigkeit des Blutserums gegenuber saurem Farbstaff bei Weilscher Krankheit sowie verschiedenen *Lebererkrankungen*. Mitt. a. d. Med. Akad. Zu Kioto, **28:** 287, 1940.

II. Qualitative protein analysis. The method of Huggins et al.[43] was used for determination of PSP binding by equilibrium dialysis. One hundred mg. phenolsulfonephthalein was dissolved in 100 cc of M/15 phosphate buffer, pH 7.4. A 15 cm. length of cellulose casing (diameter 1.75 cm.) was knotted at one end. One cubic centimeter of the above PSP stock solution and 1 cc of serum were placed in the bag and the other end knotted. The bag was immersed in a flask containing 98 cc of distilled water and attached to a rotator at 5 C for 48 hours. Equilibrium was reached in 40 hours between protein solution and dialysate. After warming to room temperature 10 cc of dialysate was diluted with water, 1 cc of 5 N NaOH added, and the volume brought to 100 cc with water. Readings were made using the Evelyn Photoelectric Colorimeter with 540 mμ filter. The colorimeter reading indicates the PSP not bound by protein within the cellulose bag. Subtraction of this figure from the standard reading of PSP yields the amount of dye bound to albumin.

The quantity of circulating serum albumin varies from day to day, from patient to patient, and from normal to disease. Consequently, as there is a variable quantity of albumin in each cubic centimeter of serum used, significant binding results are necessarily expressed as a ratio or index relating the bound PSP to weight of albumin per 100 cc. The calculation is:

$$\text{Binding Index} = \frac{\mu\text{gm of PSP bound}}{\text{Albumin Gm./100 cc.}}$$

III. Quantitative protein analysis. Albumin was determined by Howe[44] fractionation as modified by Weichselbaum[45] and nitrogen content according to the micro-Kjeldahl method of Ma and Zuazaga.[46] Correction was made for nonprotein nitrogen.

IV. Nonprotein nitrogen analysis. Determinations were made by the routine method of Folin and Wu[47] as modified by Koch and McMeekin.[48] Determinations of nonprotein nitrogen and PSP-binding were performed in duplicate.

[43] Huggins, C., Jensen, E. V., Player, M. A. and Hospelhorn, V. D.: The binding of phenolsulfonephthalein by serum and by albumin isolated from serum in cancer. Cancer Research, 9: 753, 1949.

[44] Howe, P. E.: The use of sodium sulfate as the globulin precipitant in the determination of proteins in the blood. J. Biol. Chem., 49: 93–107, 1921.

[45] Weichselbaum, T. E.: An accurate and rapid method for the determination of protein in small amounts of blood serum and plasma. Am. J. Clin. Path., 7: 40–49. 1946.

[46] Ma, T. S. and Zuazaga, G.: Micro-Kjeldahl determination of nitrogen. A new indicator and an improved rapid method. Industrial and Engineering Chemistry (Analytical Edition), 14: 280. 1942.

[47] Folin, O. and Wu, H.: System of blood analysis. J. Biol. Chem., 38: 81. 1919.

[48] Koch, F. C. and McMeekin, T. L.: A new direct nesslerization micro Kjeldahl method and a modification of the Nessler-Folin reagent for ammonia. J. Am. Chem. Soc., 46: 2066. 1924.

RESULTS

Production of reversible uremia. Five dogs were used in the experiment. Uremia was produced a total of eight times. No mortality was associated with the operation in the series. Irrespective of time interval between operation and induction of uremia the signs were uniform if the tension on the drain was sufficient to produce complete anuria. These effects were progressive weakness and apathy beginning the second day. Stupor frequently occurred by the fourth day when death appeared imminent. Coma or convulsions were not observed in the series. Voluntary fluid and food intake were moderately well maintained while in uremia but tended to be decreased with complete ureteral obstruction. No diarrhea was present but vomiting by two dogs was observed.

About 72 to 96 hours after initiation of severe uremia the angulated ureters were released. This time was varied dependent on clinical condition or concentration of nonprotein nitrogen or both. The urinary output was normal on the average of 48 hours after release of the drain. When a dog was made uremic a second time, the condition was tolerated somewhat better clinically.

For the purpose of evaluating the procedure the operation was repeated on three dogs. At the second operation the ureters were found in their normal course and not dilated. The terminal 1 cm. was occasionally adherent to the base of the bladder, but no angulation was present. Minimal ureteral dilatation was frequently observed at a third operation.

Statistically, a series of normal dogs had a mean Binding Index of 27.8 ± 4.0 with a range of 21.7–33.3. It was demonstrated that among normal dogs there was a remarkable variation in the amount of PSP bound. Normal for one was 21.7 ± 2.7, while another was 33.3 ± 4.3 with no overlap in the range. Therefore, the mean Binding Index of each normal animal is more significantly compared with its own values while in uremia. The same comparison has been followed evaluating quantitative albumin concentrations.

PSP binding by serum of dogs in uremia. A decrease in binding index was observed in each of 8 cases of experimental uremia. The average decrease was 41.6 per cent (table 1). The decrease in binding index (B.I.) was generally proportional to the elevations of nonprotein nitrogen. Minor elevations of nonprotein nitrogen were accompanied by minor depressions of B.I. Major increases of nitrogen retention had correspondingly the greatest decrease in binding of PSP to serum albumin. A uremia with nonprotein nitrogen of 100 mg. per cent had only 8.7 per cent decrease in B.I., while nonprotein nitrogens of 208 and 268 mg. per cent had decreased binding indices of 41.6 and 55 per cent respectively. With termination of uremia the decrease in nitrogen retention to normal was simultaneously accompanied by return of B.I. to normal (fig. 2). The same changes were observed in both male and female dogs. The greatest decrease observed in B.I. was in those dogs where uremia was produced the second time. This occurred irrespective of minor variations in nonprotein nitrogen. Three dogs were made uremic step-wise by gradually increasing the angulation of the ureters until complete obstruction was obtained. The expected graded variations of elevated nonprotein nitrogen and decreased B.I. were observed. Any slight release of the drain was reflected in minor improvements of binding and drop in nonprotein nitrogen.

The serum *albumin concentration* of the normal compared with uremic dogs was increased from 3.17 ± 0.3 to 3.68 ± 0.59. This 15.8 per cent increased weight accompanied all variations of B.I. and nonprotein nitrogen (table 1).

TABLE 1. *Binding index in the normal and uremic dog*

DOG NO.	NORMAL			UREMIA					
	Non protein Nitrogen mg per cent	Binding Index µgm PSP bound / Alb Gm/100 cc.	Albumin gm per cent	Uremia Number	Non-protein Nitrogen	Binding Index	Binding Index % Decrease	Albumin gm per cent	Albumin % Decrease
606	38	26.5 ± 1.1	2.91 ± 0.4	1	144	16.1	39.25	2.67	0
213	38	21.7 ± 2.7	3.2 ± 0.1	2	116	13.4	38.25	3.35	4.68
596	36	33.3 ± 4.3	3.31 ± 0.1	3	100	30.4	8.70	3.53	6.64
				4	*268*	*15.0*	54.95	4.67	41.08
697	37	23.6 ± 3.8	3.23 ± 0 2	5	122	20.2	14.41	3.96	6.5
				6	128	8.1	64.41	3.44	22.6
265	35	28.6 ± 4.5	3.2 ± 0.2	7	208	16.7	41.61	3.9	21.87
				8	170	8.9	68.88	3.94	23.12
	37	26.74 ± 4.6	3.17 ± 0.3	8	157	16.1	41.56	3.68 ± 0.59	15.81

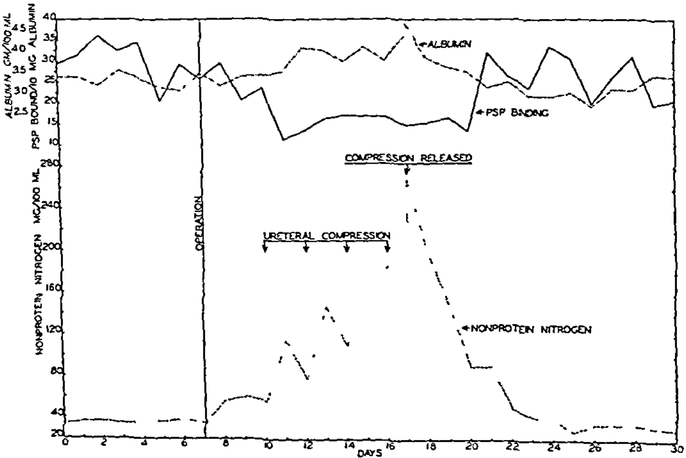

FIG 2. Demonstration of the reversible nature of qualitative and quantitative abnormalities of serum albumin in uremic dog (No. 596).

Control experiments were performed to rule out the eventuality that the observed alterations in quality and quantity of serum albumin were due to operation, anesthesia, or possible decreased food or fluid intake while in uremia:

1. Sham operation (exploratory laparotomy) demonstrated a slight decrease in B.I. which returned to normal by the fourth postoperative day (table 2).

2. A dog was anesthetized with ether for two hours. Serum analyses of the first and second postanesthetic days revealed no quantitative or qualitative abnormality of albumin compared to the same preanesthesia period (table 2).

3. Dehydration for periods of five and nine days failed to produce decrease in B.I. or increase in concentration of serum albumin.

4. A period of complete dehydration and starvation was studied with apparently no significant alteration of B.I. or albumin concentration until the third day (table 3). Following complete ureteral obstruction uremic dogs developed decreased food and fluid intake. However, the average time for complete anuria to maximum decrease in B.I. and release of the drain was only 1.4 days.

TABLE 2. *Effect of operation and anesthesia on binding index*

I. Operation	
Normal Binding Index	21.7 ± 2.7
One hour laparotomy	
First postoperative day	15.8
Second postoperative day	16.4
Third postoperative day	19.0
Fourth postoperative day	21.4
II. Anesthesia	
Normal Binding Index	31.1 ± 2.8
Two hour ether anesthesia	
After one hour anesthesia	26.0
First postanesthetic day	30.7
Second postanesthetic day	29.8

TABLE 3. *Effect of dehydration and starvation on binding index*

	BINDING INDEX	ALBUMIN—GM PER CENT	HEMATOCRIT PER CENT
I. Dehydration			
A. Normal	27.5 ± 4.4	3.6 ± 0.2	46
No fluids nine days			
Fifth day	29.9	3.61	46
Ninth day	34.0	3.38	52
B. Normal	30.3 ± 2.5	3.53 ± 0.6	
No fluids four days			
First day	32.6	3.53	
Second day	33.2	3.62	
Third day	32.9	3.5	
Fourth day	33.0	3.18	
II. Starvation and Dehydration			
Normal	27.5 ± 4.4	3.6 ± 0.2	
No fluids or food six days			
First day	23.5	3.62	
Second day	22.9	3.71	
Fourth day	14.8	4.05	
Fifth day	20.4	3.93	
Sixth day	21.2	3.56	

PSP binding by serum of humans in uremia. The clinical series studied consisted of 25 consecutive patients in uremia. Primary diseases were: urinary obstruction of various etiology 12, glomerulonephritis 3, lower nephron nephrosis 3, arteriosclerosis 3, nephrosclerosis 2, polycystic kidneys 1, and atrophic pyelonephritis 1.

The age range was from 8 months to 87 years; sex distribution was 11 female and 14 male (table 4).

TABLE 4. *Decrease binding index of humans in uremia*

UREMIA #	UNIT #	AGE	SEX	DIAGNOSIS	NON-PROTEIN NITROGEN[1]	BINDING INDEX[2]	BINDING INDEX DECREASE %	ALBUMIN[3]
1	468813	13	M	Congenital bilateral megalo-ureter and hydronephrosis	76	31.4	44.91	5.26
2	361422	4	F	Congenital bilateral megalo-ureter and hydronephrosis	57	31.4	44.91	4.67
3	483189	8 Mo.	M	Congenital hydronephrosis	168	19.2	66.32	4.17
4	251550	35	F	Polycystic kidneys	65	17.8	68.77	4.21
5	476834	62	M	Bilateral ureteral obstruction; carcinoma rectum	148	39.4	30.88	3.55
6	399381	62	F	Bilateral hydronephrosis	345	11.6	79.65	6.02
7	476353	56	M	Bilateral ureterosigmoidostomy; carcinoma bladder	98	33.8	40.70	4.74
8	397185	67	F	Bilateral ureterosigmoidostomy; carcinoma bladder	67	31.2	45.26	4.17
9	418951	36	F	Bilateral hydronephrosis	99	24.6	56.84	4.06
10	174359	72	M	Bilateral renal calculi	60	35.8	37.19	3.77
11	199085	56	F	Bilateral renal calculi	50	43.0	24.56	3.37
12	367839	56	F	Unilateral kidney with multiple calculi	79	27.4	51.93	4.09
13	480926	5	M	Nonfunctioning left kidney; hydronephrosis, right	70	35.7	37.37	3.78
14	470175	58	F	Bilateral atrophic pyelonephritis	70	32.3	43.33	4.02
15	478836	50	M	Lower nephron nephrosis (post transfusion)	150	20.1	64.74	4.36
16	27424	44	M	Lower nephron nephrosis (post transfusion)	200	32.8	42.46	3.97
17	483276	53	M	Lower nephron nephrosis (prolonged hypotension)	115	22.6	60.35	3.96
18	481389	22	M	Glomerulonephritis	198	17.8	68.77	4.22

TABLE 4—*Continued*

UREMIA #	UNIT #	AGE	SEX	DIAGNOSIS	NONPROTEIN NITROGEN[1]	BINDING INDEX[2]	BINDING INDEX DECREASE %	ALBUMIN[3]
19	483045	59	F	Chronic glomerulonephritis	135	25.0	56.14	4.40
20	456230	62	M	Chronic glomerulonephritis	105	26.9	52.81	4.08
21	344365	63	M	Nephrosclerosis; hypertension	190	13.8	75.79	4.70
22	468122	58	M	Arteriosclerotic cardiovascular disease; benign hypertrophy prostate	120	23.1	59.47	4.12
23	351672	75	M	Arteriosclerotic cardiovascular disease	90	21.7	61.93	4.37
24	214445	87	F	Arteriosclerosis; fracture femur	71	22.6	60.35	3.99
25	483724	53	F	Nephrosclerosis; hypertension; diabetes mellitus	182	20.9	63.33	4.31
Mean					120.3	26.5 ± 8.1	53.55 ± 14.7	4.25 ± 0.5

[1] Nonprotein nitrogen normal 25–35 mg. per cent.

[2] Binding index, normal 57 ± 5.8 from Huggins;[43] Amount of PSP bound per 10 mg. of albumin.

[3] Albumin, normal 4.7–5.7 Gm./100 cc. serum.

The normal mean B.I. is 57. In uremic patients the mean B.I. was 26.5 or a decrease of 53.6 per cent. There was a decreased B.I. in each case of uremia despite the nature of the underlying disease producing the uremia.

The changes observed in uremia in the clinical cases and the laboratory animals were nearly identical. Minimal degrees of uremia were characterized by minor decrease in dye binding. A nonprotein nitrogen of 50 mg. per cent was accompanied by a B.I. of 43.0 (24.6 per cent decrease). Severe uremia was accompanied by a major decrease in B.I. A case with nonprotein nitrogen of 345 mg. per cent had a B.I. of 11.6 (79.7 per cent decrease).

In general variations of B.I. did not follow the clinical signs and symptoms but were directly proportional to nonprotein nitrogen concentration. Decrease in binding of serum albumin in uremia was as marked at age 8 months as in the sixth and seventh decade. Sex difference had no effect on B.I.

The increase in albumin concentration in the uremic animal is not consistently observed in the patient with uremia.

DISCUSSION

All clinical and laboratory data establish a decreased PSP-binding of serum albumin in uremia. There is a 54 per cent decrease of binding index in humans and a 42 per cent decrease in dogs. An altered albumin is therefore present.

This pathological albumin indicates another fundamental derangement of the human and animal organism in uremia. The altered albumin is present irrespective of the etiological factor or disease producing uremia. The change in protein is unrelated to age or sex.

In general the variations of B.I. are proportional to and concurrent with the degree of uremia as measured by the nonprotein nitrogen concentration. In the canine study of preuremic, uremic and posturemic phases, however, the binding index occasionally tends to lag 12 to 24 hours behind variations of nonprotein nitrogen. There was also a 15 per cent increase in quantitative albumin concentrations which was not observed in human uremia.

It has been frequently observed that the human suffering with prolonged uremia tolerates tremendous levels of nonprotein nitrogen with the same clinical appearance as another patient with acute uremia and lower nonprotein nitrogen. Though accommodation is attempted by the organism, this certainly is not reflected in chemical analyses of the blood. The marked decrease in B.I. and the elevation of nonprotein nitrogen present the true gravity of the uremia. This phenomenon may also be observed in the animal repeatedly made uremic. Dogs in uremia for the second time clinically tolerate the condition somewhat better. The greatly increased quantity of defective serum albumin affords a more accurate appraisal of the second uremic status.

The findings of this study have been presented. Mention may be made of preliminary investigations of the abnormal protein observed in uremia. This entails an understanding of the normal sites of attachment of phenolsulphonphthalein on the exceedingly complex albumin molecule. The molecular weight of albumin is 69,000; the molecular structure is unknown. The molecule is basically composed of 18 amino acids. Brand[49] indicates the total number of molecules of these amino acids in albumin is well over 551. Klotz[50] postulates a total of 22 locations where methyl orange (a dye similar to PSP) may be attached to albumin.

In uremia, binding of PSP to albumin is decreased. This may indicate an intrinsic defect or chemical change of the albumin molecule. Huggins et al.,[43] however, fractionated albumin with altered dye binding and only the composition of normal albumin was present. In addition he found that as early as 8 hours after operation a decrease in dye binding occurred. The speed with which the abnormality of the protein develops and the normal basic composition of the molecule preclude any fundamental defect. Evidence supports the view that in uremia the loci of attachment normally occupied by PSP are unavailable, causing the decrease in dye binding. The most acceptable possibility is another molecule may be bound by serum albumin. Such a change would be immediate and superficial. Further, Klotz[51] has definitely established that competitive binding does occur with albumin. The precise competing group in uremia is not known.

[49] Brand, E.: Amino acid composition of simple proteins. Ann. N. Y. Academy of Sc., 47: 187-228, 1946.

[50] Klotz, I. M., Walker F. M. and Pivan, R. B.: The binding of organic ions by proteins. J. Am. Chem. Soc., 68: 1486, 1946.

[51] Klotz, I M., Triwush, H. and Walker, F. M.: The binding of organic ions by proteins. Competition phenomena and denaturation effects. J. Am. Chem. Soc., 70: 2935, 1948.

In vitro experiments producing model uremia by addition of large concentrations of urea, uric acid, creatinine, creatine, guanidine and phenol to normal human serum have failed to produce an albumin abnormal in PSP binding. In vivo concentrations of these same nitrogenous products have been administered intravenously to dogs over periods of 3 to 5 hours to produce uremic blood levels. There has been no significant alteration of the albumin in the time predicted for these changes to occur. These findings support the theory that increased concentration of nonprotein nitrogen per se does not apparently act directly on albumin to produce the abnormality present in uremia. This does not preclude the possibility of an indirect mechanism.

Streicher[52] observed that prolonged intravenous administration of 5 to 10 per cent urea solution was fatal to dogs. Bollman[53] demonstrated that in the dog the liver is necessary for urea formation. Hartman[55] perfused the small intestine of dogs with urea resulting in acute parenchymatous destruction of the liver. Defective liver function tests in uremia are well recognized. Becher[54] observed increased concentration of phenolic bodies in uremia. The failure of the detoxicating function of the liver permits this accumulation of free phenols.

TABLE 5. *Effect of repeated ether—25 C extraction on serum from humans in uremia*

	PSP BINDING	ALBUMIN	TOTAL PROTEIN	BINDING INDEX (B I.)	PER CENT INCREASE B I.
	gm	*Gm/100 ml.*	*Gm/100 ml.*		
Normal					
Pre-extraction	255	5.20	6.98	49.1	
Post-extraction	260	5.05	6.79	51.1	3.9
I. *Uremia*					
Pre-extraction	80	6.02	7.72	13.3	
Post-extraction	105	5.82	7.46	18.0	26.1
II. *Uremia*					
Pre-extraction	90	4.36	7.76	20.6	
Post-extraction	140	4.08	7.26	34.3	40.0

The possibility exists that in uremia the increased concentration of one or more nonprotein nitrogenous products produces fatty degeneration or other significant changes of the liver. A liver so damaged may elaborate a fat or lipid bound to serum albumin. This would render the usual binding locations unavailable for PSP and cause the decreased binding of uremia. The investigations of Luck and his group[56] prove that fatty acids combine with albumin and that any free fatty acid in the circulation probably exists in combination with serum albumin. The increased concentration of blood lipids in uremia is also recognized.[58]

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[52] Streicher, M. H.: Experimental uremia; uremic enteritis Arch. Clin. Med., **42:** 835, 1928.

[53] Bollman, J. L. and Mann, F. C.: Studies on the physiology of the liver XVIII The effect of removal of the liver on the formation of ammonia Am. J. Physiol , **92:** 92, 1930.

[54] Becher, E.: Pathogenese, Symptomatologie und Therapie der Uramie. Ergebnisse der gesamten Medizin, **18:** 51, 1933.

[55] Hartman, F. W.: Methods and effects of increasing the urinary constituents in the body. J. Exper. Med., **58:** 649, 1933.

[56] Boyer, P. D., Ballou, G A and Luck, J. M.: The combination of fatty acids and related compounds with serum albumin. III. The nature and extent of the combination J Biol. Chem., **167:** 407, 1947.

As a result of these various data serum from humans in uremia was repeatedly ether extracted at −25 C by the method of McFarlane.[57] In the two cases studied there were 26 and 40 per cent increased PSP-binding of serum albumin (table 5). An ether soluble compound, probably a lipid, was apparently removed from the albumin molecule. As a consequence there were more available loci on the albumin for binding by PSP.

Though it is impossible at this time to defend the view that in uremia there is liver degeneration with a lipid bound to serum albumin resulting in decreased PSP binding, still the preliminary evidence presented warrants further investigation in this direction.

SUMMARY

A new and simple method is described for the production or reversible experimental uremia which permits immediate termination of the uremia by simple nonoperative intervention. Since a specific degree of uremia and recovery therefrom may be obtained as desired, the method is useful for investigation of renal insufficiency. The return to normal of clinical and chemical observations demonstrate the reversible feature of the technique. As only one operation is necessary to repeatedly produce uremia in a laboratory animal, the procedure may be considered practical for repeated observations over a long period of time.

This procedure was designed and applied to a study of the serum proteins of uremic dogs; the findings concerning the serum proteins were also confirmed in a series of patients in uremia of various etiologies.

The data presented demonstrated that in uremia there is an altered serum albumin as determined by impaired ability to bind the dye phenolsulfonephthalein. This alteration of albumin is both of quality and quantity.

In the clinical and laboratory series studied this pathological protein was consistently present. Further, it is unrelated to age or sex and is generally directly proportional to the degree of uremia.

The abnormality of serum albumin is apparently independent of either the etiological factor producing the uremia or the anatomical renal unit involved.

The nature of the change in the albumin molecule is discussed.

The author would like to acknowledge deep appreciation to Professor Charles Huggins for the privilege and pleasure of working in his laboratory, his constantly available counsel and his guidance in basic research.

[57] McFarlane, A. S.: Behavior of lipoids in human serum. Nature, **149**: 439, 1942.

[58] Mendoza, H. C. and Diaz, C. J.: Fats of plasma after ligature of the ureters. Bull. of the Institute for Med. Res., **2**: 239, 1949.

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DISCUSSION

Dr. Clarence G. Bandler (New York, N. Y.): The originality of Dr. Roger Baker in producing reversible uremia in dogs is most ingenious and highly commendable. The presentation well merits the prize awarded by our association and I most assuredly wish to add these words of approbation.

Dr. Baker's technique of applying a Penrose drain simultaneously to both ureters with fixation to the abdominal wall has enabled him to produce even and equal compression of the ureters resulting in obstruction to the urinary output of the kidneys, causing uremia. This condition is readily reversible by releasing the compression, with no permanent damage to the animals. Thus, Dr. Baker has been able to repeat these experiments on the same dogs.

Stimulated by the work of Marshall and Vickers of Johns Hopkins University, who demonstrated that phenolsulfonphthalein has an affinity for binding with serum albumin and other constituents of blood, Dr. Baker has evolved a binding index which has definite clinical application. However, it should be noted from the experimental uremia that the decrease in the binding index (B.I.) lags from 12 to 24 hours behind the increase in nonprotein nitrogen. Hence, for practical clinical purposes, it may be assumed that nonprotein nitrogen (N.P.N.) is a more sensitive indicator of the uremic state than is the binding index (B.I.).

In his summation the doctor states that "the data presented demonstrated that in uremia there is an *abnormal serum albumin* as determined by impaired ability to bind the dye phenolsulfonphthalein." I think that the choice of the term "abnormal serum albumin" is an unhappy one. I do not believe that the doctor actually means this, because in his discussion he quotes Huggins, et al., who fractionated albumin with altered dye binding, and only the composition of *normal* albumin was present. Moreover, he quotes Klotz who definitely established that competitive binding for albumin occurs and that the precise competing group in uremia is not known. It is possible, as Dr. Baker states, that lipids may become attached to the serum albumin in uremia, thus decreasing its binding properties for the dye (PSP). In view of all of this, I think the term "abnormal serum albumin" carries an incorrect connotation. It seems to me that it would be more correct to state that in uremia the serum albumin *partially loses* its binding power for phenolsulfonphthalein. This decrease in binding index probably is due to competitive adsorptive phenomena which occur in the uremic state.

In this possible association of lipids and albumin, as suggested by the author, there appears to be a fruitful field for further investigation. Many researches into the basis of uremia have failed to disclose the underlying factors which produce the clinical state. Perhaps, this lies not in those products associated with failure of renal excretion, but does lie in the province of abnormal liver function. If liver degeneration can be established to be present in uremia, we may very well have the explanation for the so-called "hepatorenal syndrome" which is alluded to so often in medical writings. Indeed we may find that the clinical picture of uremia can be ascribed to liver toxicity and not to renal failure per se. This concept warrants future experimental and clinical research and it is to be hoped that the author will pursue his investigative leads.

I cannot limit my praise for the excellent contribution of Dr. Baker and I can foresee that further animal experimentation along the lines so definitely established will lead to many worthwhile observations of considerable clinical importance.

DR. ROGER BAKER (Chicago, Ill.): I wish to again express my appreciation to the American Urological Association. Also I wish to thank Dr. Clarence Bandler for his kind and instructive discussion. I agree that this is not an intrinsic abnormality of the albumin molecule itself. It is present however in a pathological condition, that of uremia, irrespective of the renal unit or etiological factor involved. As Dr. Bandler has mentioned, fractionation of this altered albumin molecule reveals it to be completely normal. Some molecule is apparently linked or superfically bound to it in this disease state.

The appearance of this abnormality of serum albumin lags slightly behind the rise of NPN. Increased concentrations of nonprotein nitrogenous products are necessary to first damage the liver and then produce the results observed.

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RETROCAVAL URETER: REPORT OF FOUR CASES AND REVIEW OF LITERATURE

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Since Hochstetter[1] in 1893 first described retrocaval ureter in man, 40 cases have been reported. Of these, only 18 cases were observed antemortem, 12 being discovered at surgery and only 6 have been diagnosed preoperatively. Twenty-two cases were observed either in postmortem examination or at the anatomical dissection table. The vast majority of cases have occurred in males; only 8 have been reported in the female. In every instance, except one, the acardiac monster of Gladstone, the lesion has occurred on the right side. In Gladstone's case, the lesion was bilateral.[2]

The apparent rarity of this entity must be contributed to by unfamiliarity with its existence for as Creevy has stated, the pyelographic course of the ureter is so typical that once seen it is not easily forgotten.[3]

The incidence in dissections was reported as follows:

Dial—1936	1:1600 cadavers[4]
Adachi—1937	2:1055 adults
Pick-Anson—1940	1:570 cadavers[5]
DeCarlo—1949	1:4185 (bodies at the Daniel Baugh Institute of Anatomy).

DeCarlo further points out that the preponderence of males in the postmortem cases at least was ascribed partly to the fact that relatively few female bodies were assigned for routine dissection.[6]

Familiarity with the condition is significant in its recognition, for despite the apparent rarity, several authors have reported 2 cases: Gladstone,[2] Jacobson,[7] Rotter,[8] Randall and Campbell[9] and Derbes and Dial.[4] Derbes reported still a third case.[10]

We are herewith reporting 4 cases. Three have been confirmed surgically and in one we have pyelographic evidence only. However, by studying the pyelograms of all cases reported thus far, we are convinced that this fulfills the pyelographic criteria for the diagnosis of retrocaval ureter.

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[1] Hochstetter, F.: Anat. Anz., **3:** 938–940, 1888.
[2] Gladstone, R. J.: J. Anat. Physiol., **40:** 71080 (3rd series), 1905.
[3] Creevy, C. D.: J. Urol., **60:** 26–30, 1948.
[4] Derbes, V. J. and Dial, W. A.: J. Urol., **36:** 226–233, 1936.
[5] Pick, J. W. and Anson, B. J.: J. Urol., **43:** 672–685, 1940.
[6] DeCarlo, J.: J. Urol., **45:** 827–831, 1941.
[7] Jacobson, V. C.: Arch. Path. and Lab. Med., **3:** 302–311, 1927.
[8] Rotter, H.: Ztschr f. anat. u. Entwicklgesch, **104:** 456, 1935.
[9] Randall, A. and Campbell, E. W.: J. Urol., **34:** 565–583, 1935.
[10] Derbes, V. J. and Lanasa, M. J.: Urol & Cutan, Rev., **41:** 172–175, 1937.

DEFINITION

This is a congenital anomaly of the venous vascular tree resulting in an abnormal course of the ureter which instead of passing lateral to the vena cava passes behind it, partially encircles it for a short distance and then pursues its normal course ventral to the vena cava down into the bony pelvis and thence to the bladder.

Because of its position it has been called retrocaval ureter, postcaval ureter, circumcaval ureter, deflected ureter and preureteric vena cava. In urologic texts, it is classified often under vascular abnormalities rather than ureteral anomalies.

Hydronephrosis has developed in three-fourths of the cases, usually in adult life, demonstrating the low grade obstruction present.

Although this type of anomaly has been quite common in laboratory animals, especially the cat, hydronephrosis has never been reported in quadrupeds. This has been attributed to the fact that the vena cava falls away from the ureter in the quadruped thus producing little or no obstruction to ureteral urinary outflow.

EMBRYOLOGY

Pick and Anson[5] point out that during fetal life the permanent kidney (metanephros) ascends from the pelvis to the loin passing through a ring of veins, the perimetanephric or peri-ureteric ring. The kidneys attain their normal position in the loin about the twentieth week of fetal life.

Ventrally, this ring is formed by the lumbar division of the postcardinal vein and the anastomosis of the subcardinal and postcardinal veins, as described by McClure and Butler[11] in 1925, and the sacrocardinal vein, according to Gruenwald, 1938.[12]

Dorsally, the ring is made up of the lumbar division of the supracardinal vein and the subcardino-supracardinal anastamosis (McClure and Butler) or the sacrocardinal vein of Gruenwald.

Normally, the postrenal portion of the inferior vena cava arises from the dorsal limb of the perimetanephric ring, the ureter thereby lies antecavally.

Abnormally the following will result:

1) The ureter will be postcaval if the ventral limb rather than the dorsal persists or if the dorsal limb fails to develop.
2) If both limbs persist the ureter will pass between cavae.

Thus failure of atrophy of the postcardinal system of veins (or persistence of the postcardinals) is an accepted embryological explanation of this anomaly. Except for Gladstone's case of bilateral retrocaval ureter all cases have been right sided. In the cat, bilaterality has been noted in 20 cases or 3.3 per cent (Darrach—1907) as quoted by Pick and Anson.[5]

Huntington and McClure describe 15 types of potential inferior vena cavae and have observed all but three in the cat.[13]

[11] McClure, C. F. W. and Butler, E. G.: Am. J. Anat., 35: 331–384, 1925.
[12] Gruenwald, P. and Surks, S. N.: J. Urol., 49: 195–201, 1943.
[13] Quoted by Antopol W. and Yelin, G.: Urol. & Cutan. Rev., 43: 746–752, 1939.

Designating the right and left posterior cardinal vein by the letters A and D respectively, the right and left subcardinals B and C, they enumerated the possible combinations that may occur as follows: A, AB, ABC, ABCD, ABD, AC, ACD, AD, B, BC, BCD, BD, C, CD and D. The normal adult vena cava is B. There are four general groups in humans therefore (fig. 1):

1. Bilateral postcaval ureters, bilateral persistence of the postcardinal vein, Type AD, Gladstone's case is the only one so far.
2. Right sided postcaval ureter.
   A. Single vena cava: This is due to unilateral persistence of the posterior cardinal vein, the postrenal segment of this vein forming the post cava. This is type A and is the most common type.

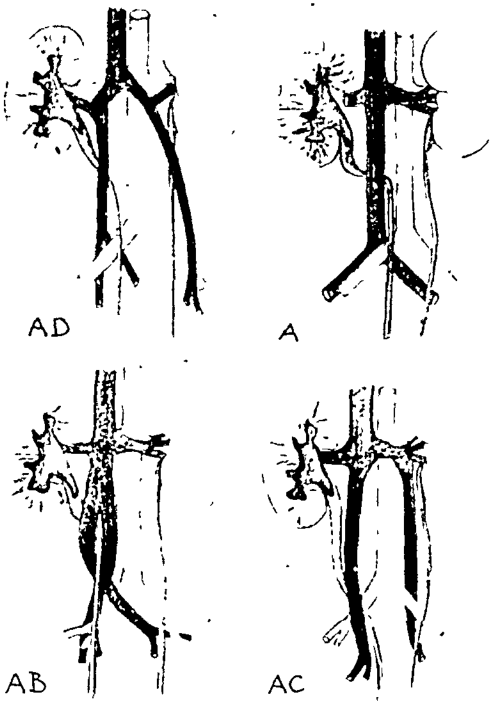

FIG. 1. Four varieties of retrocaval anomalies in man. (After Huntingdon and McClure.)

   B. Double vena cava, both on the right side: In this form, the ureter passes through a ring formed by the two vessels and their anastomoses. This is due to unilateral persistence of the right posterior cardinal together with the postrenal portion of the right supracardinal, giving a double cava, both on the right side, with the ureter passing through the venous ring. This is type AB and is infrequent.
   C. Double vena cava, one on the right and one on the left. The right ureter crosses behind the corresponding vein. This is due to unilateral persistence of the right posterior cardinal and left supracardinal veins so that double post cava persist one on each side with the ureter passing dorsal to the right vein. This is type AC and is quite rare.

CLINICAL FEATURES

Graves and Davidoff,[14] in 1922, observed this type of ureter in the rabbit and then in the cat and decided it was of clinical interest inasmuch as it was reported in humans and was a potential cause of hydronephrosis.

Unfortunately, there are no symptoms pathognomic of postcaval ureter. Usually, the symptoms are those of obstruction sometimes complicated by symptoms of infection or of stone.

All operated cases have had hydronephrosis which was the reason for surgery.

Life is not incompatible with it for not all cases develop hydronephrosis.

If sufficient time elapses, it is probable that hydronephrosis from ureteral compression would occur in every instance. The mechanism may be compression alone or by kinking or stricture due to the anomalous course of the duct.

Symptomatology has varied from no symptoms at all to severe renal colic with sharp pain radiating along the ureter. Frequency, following each attack, may occur. Nocturia is often seen. Hematuria, either gross or microscopic, has been a fairly constant feature. Pyuria has been frequent with secondary infection or stone.

Age is a factor. It has not been reported clinically below the age of 12, the time element for the development of hydronephrosis being important here. Hydronephrosis is the rule in older patients.

Pregnancy may intensify the symptoms and apparently hastens the obstructive pathological process. Four of seven women discussed by Pick and Anson gave a history of earlier pregnancy.

Hypertension has been reported, but it is apparently a coincidental finding associated with other pathological change such as nephrolithiasis, etc.

Hematuria and loin pain in the cases operated on have existed for variable periods from 7 years to a few weeks.

Although the symptoms are not pathognomonic, nevertheless one must always consider the possible existence of retrocaval ureter in a right sided hydronephrosis.

DIAGNOSIS

Postcaval ureter should be considered a possibility in all cases of right hydronephrosis (DeCarlo).[6] Its x-ray features are so distinctive as to be almost pathognomonic (Harbach).[15]

Failure to recognize the entity is only due to unfamiliarity with its existence (Creevy).[3]

As Pick and Anson[5] have pointed out, the surgeon who uses a lumbar incision in exploration will not observe the entire abdominal course of the ureter and may miss the obstructive factor at the vena cava. Accordingly, entire diagnostic reliance must be placed upon x-ray studies for the proper preoperative diagnosis and subsequent corrective surgery.

Anteroposterior, lateral and oblique x-rays, ureteral catheterization with radioopaque catheters, retrograde ureteropyelography and excretory urograms with steroscopic ureterograms, and x-rays in prone, upright and lateral positions have all been tried and each lends corroborative information. The distinctive roentgenographic features are as follows:

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[14] Graves, R. C. and Davidoff, L. M.: J. Urol., 8: 75–80, 1922.

[15] Harbach, F. O.: N. Y. State Med. Jour., 40: 800–802, 1940.

Anterior ureteropyelography reveals hydronephrosis with a very long proximal segment of the ureter involved. In addition, the ureter is dislocated medially to or beyond the midline, beginning with the third, fourth, or fifth lumbar vertebrae.

The resultant redundancy from obstruction and hydronephrosis produces a characteristic hook and a distinct sickle shape or S-curve is imparted to the ureter.

After the ureter has passed around the cava, it comes downward into the pelvis with a normal course and caliber. The medial portion of the ureter is undilated.

In oblique and lateral views, the retrocaval ureter hugs the spinal column instead of falling away from it.

As Mertz and Hamer[16] have indicated in lateral view, the ureter becomes anterior to the vertebral bodies at about the third lumbar vertebra. This third dimension view is an added measure in the diagnosis. This sign has been almost pathnomonic in a high per cent of cases (24 of 27) reported by Pick and Anson[5] in 1940. It does not apply, however, in cases of unilateral double cava in which the ureter passed between the two veins and was a normal distance from the vertebrae.

Goyanna and Cook[17] believe that retrograde study with the opaque x-ray catheter is the most useful method. This depicts the abnormal course of the ureter quite accurately.

Creevy, whose opinion we share, states that ordinary ureteropyelography is sufficient; that once seen this picture is so characteristic it is not easily forgotten.

SURGICAL CONSIDERATIONS

Surgical therapy has consisted of nephrectomy in the far advanced cases and attempts at renal conservation in the cases with a partially damaged kidney.

These attempts at conservation may be classified as follows:

1. Division of the hydronephrotic segment above the ureteropelvic outlet, carefully withdrawing the detached segment from behind the vena cava and then anastomosing it anterior to the vena cava. This was first proposed by Harrill[18] in 1940 and is the procedure of choice. The rationale in dividing the pelvis here is to have a tube of greater diameter to anastomose thus lessening the possibility of postoperative stricture.
2. Ureteropelvic anastomosis: The ureter is divided at the ureteropelvic junction, unwound from the vena cava and anastomosed in its normal position. This was proposed by Derbes and Dial[4] in 1936.
3. Division of the ureter just below the ureteropelvic junction. This may be done transversely or obliquely. The oblique repair was done by Kim-

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[16] Mertz, H. O. and Hamer, H. G.: J. Urol. 31: 25–55, 1934.
[17] Goyanna, R., Cook, E. N. and Counseller, V. S.: Proc. Staff Mayo Clinic, 21: 356–360, 1946.
[18] Harrill, H. C.: J. Urol., 44: 450–457, 1940.

brough,[19] the first surgeon to successfully correct this anomaly. Ureteral division below the ureteropelvic junction was to avoid stricture at the ureteropelvic junction.

4. Division of the ureter at its entry into the bladder wall, removing the ureter from behind the vena cava and placing it in its normal relationship to the vena cava and then reimplanting the distal end in the bladder wall. This was advocated by Lowsley[20] to preserve the intrinsic nerve supply. This led to an impermeable stricture of the terminal ureter with a fistula above it.
5. Division of the ureter and excision of a diseased segment (from fibrosis, infection) passing behind vena cava and then performing an end-to-end ureteral anastomosis anterior to the vena cava. This was performed by Goyanna, Cook and Counseller.[17]

There have been eleven attempts to correct this anomaly surgically: Kimbrough,[19] May,[21] Uebelhoir,[22] Harrill,[18] Greene and Kearns,[23] Goyanna et al.,[17] Nourse and Moody,[24] Lowsley,[20] Creevy,[3] Austen and Olson,[26] and Shearer.[25]

The case of Nourse and Moody later required nephrectomy and Lowsley's case developed stricture and fistula.

There are thus eight instances of successful surgical repair of this condition. The longest follow-up, 3 years, has been that reported by Creevy.

Some of the dangers and difficulties in the repair include marked narrowing of the ureter where it is wound about the vena cava. The narrowing may be so marked as to interfere with drainage after the anastomosis has been made.

Removal of adhesions at the uretero-vena caval attachment may strip the local ureteral blood supply and interfere with proper healing of the anastomosis. The vena cava may be torn where adhesions to it and ureter are dense, formerly considered a serious complication. Now elective vena caval interruption is not unusual. In type AB division (fig. 1) of the anterior limb of the vena cava may obviate any ureteral surgery if the ureteral lumen is adequate.

CASE REPORTS

Case 1. A.H. case No. 70444, M. T., a 40 year old white housewife, was admitted to the urological service May 2, 1940, complaining of recurrent attacks of right costovertebral angle pain with radiation to the right iliac crest. These attacks lasted 4 to 5 days and were associated with frequency, chills and fever.

The patient was obese. The temperature was normal, pulse 100, respiration 20, blood pressure 200/120. The heart was enlarged to the left. There were no abdominal masses. The urine was cloudy with 2 plus albumin, 2 to 3 red blood cells and 10 to 15 white blood cells per high power field. Nonprotein nitrogen was 45 mg. per cent. All other laboratory studies were normal.

The right kidney was not visualized on excretory urography.

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[19] Kimbrough, J. C.: J. Urol., **33**: 97-107, 1935.

[20] Lowsley, O. S.: Surg. Gynec. & Obst., **82**: 549-556, 1946.

[21] May, F.: Ztschr. f. Urol., **32**: 316, 1938.

[22] Uebelhoer, R.: Ztschr. f. Urol., **30**: 767-772, 1936.

[23] Greene, L. F. and Kearns, W. M.: J. Urol., **55**: 52-59, 1946.

[24] Nourse, M. H. and Moody, H. C.: J. Urol., **56**: 525-529, 1946.

[25] Shearer, T. P.: J. Urol., **63**: 152-158, 1949.

[26] Austen, A., and Olsen, R.: Personal communication, 1949.

On cystoscopy, cloudy urine with numerous pus cells was obtained from the right kidney; the phenolsulfonphthalein excretion was poor from that side.

Retrograde pyelography revealed marked dilatation of the pelvis and calyces of the right kidney, consistent with pyonephrosis. The upper ureter was displaced toward the midline and described an upward course before descending toward the bladder. This suggested obstruction due to an aberrant vessel (fig. 2, *A*).

Exploration of the right kidney through a lumbar incision revealed a kidney with a markedly dilated pelvis and dilated proximal ureter.

Dilatation was found to be due to compression of the ureter by the inferior vena cava behind which the ureter passed. A nephrectomy was performed as the kidney was essentially functionless.

Except for a mild wound infection the patient had a benign postoperative course. Her blood pressure which had been sustained at 200/120 dropped to 150/80 following nephrectomy and remained at that level. A urethral stricture was dilated and the patient was discharged on the twenty-second postoperative day with the final diagnosis of pyonephrosis, right, due to retrocaval ureter.

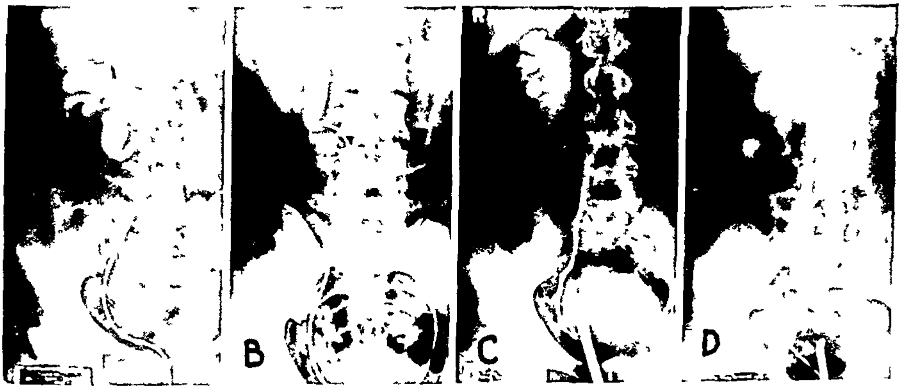

FIG 2

Case 2. A.H. No. 73719, K. M., a 39 year old white caretaker, was admitted to the urological service August 4, 1940, complaining of pain in his left side of 3 months' duration. This followed the lifting of a heavy object. Grossly bloody urine lasted 36 hours, and was followed by pain in the left and right flanks. The patient had lost 17 pounds.

Physical examination revealed a flat abdomen with slight rigidity in the right upper quadrant. The right kidney was enlarged and tender.

Urinalysis revealed an occasional red blood cell. All laboratory studies were normal.

Excretory urography disclosed that the right renal pelvis was dilated to a point opposite the third lumbar vertebra. At this level, the ureter turned sharply upward upon itself toward the midline and then proceeded directly downward in a normal manner. Retrograde studies confirmed the abnormal course of the ureter (fig. 2, *B*).

The findings were characteristic of retrocaval ureter. The patient refused further treatment and signed out of the hospital against advice.

The urograms were absolutely pathognomonic of retrocaval ureter and the senior author testified to this effect in court when the patient sought compensation for his alleged injury while lifting.

Case 3. A.H. No. 83230, M. D. P., a 37 year old white man, was admitted to the urological service June 2, 1941, complaining of constant, dull, low backache of 2 years' duration. He had been voiding grossly bloody urine for 48 hours prior to admission.

Physical examination was essentially negative except for bilateral inguinal lymphadenopathy.

The urine revealed numerous red blood cells per high power field.

The plain urogram demonstrated a calcific density in the region of the left kidney. The excretory urogram showed an enormously dilated right kidney pelvis and calyces with a marked degree of proximal hydro-ureter.

On cystoscopy, the ureters were readily catheterized; the urine from the right renal pelvis contained numerous red blood cells. Phenolsulfonphthalein excretion from the right was 12 per cent in 15 minutes; 5 per cent from the left.

Right retrograde pyelograms revealed marked hydronephrosis and hydroureter extending down to the level of the transverse process of the fourth lumbar vertebra. At this point the ureter looped cranially and then passed toward the midline across the vertebral bodies and then descended in normal fashion (fig. 2, *C*).

A preoperative diagnosis of stone in the lower calyx of the left kidney and right hydronephrosis due to retrocaval ureter was made.

A left nephrolithotomy was performed on the fifth hospital day.

Thirteen days later the right kidney was explored and the preoperative diagnosis of retrocaval ureter was confirmed. The extrarenal portion of the pelvis was found to be markedly dilated as was the proximal portion of the ureter.

The ureter passed behind the inferior vena cava just caudad to the origin of the right renal vein from the cava. After passing behind the vena cava the ureter coursed over the ventral surface of the cava and thence down into the pelvic cavity.

The renal parenchyma was in good condition and a plastic reparative procedure was decided upon.

The renal pelvis and proximal ureter were dissected free from the surrounding structures with great care exercised in dissecting the ureter from the vena cava. The pelvis was then divided 2 cm. proximal to the ureteropelvic junction. The distal pelvis and attached ureter were then brought anteriorly from behind the vena cava and the divided segments anastomosed. A nephro-ureterostomy tube with the ureteral portion well down the ureter was introduced and the wound closed.

The next day, the patient's temperature rose to 103 F and crepitation was felt in the anterior end of the incision. The wound was opened in several places and cultures taken. Gas gangrene antitoxin was given locally and parenterally plus sulfathiazole and intravenous fluids. The cultures were reported negative for Cl. welchii and the patient's convalescence was subsequently normal.

The nephro-ureterostomy tube was removed 2 weeks postoperatively with normal wound healing.

Retrograde studies revealed hydronephrosis of lesser degree with a higher ureteropelvic junction than before.

Excretory urograms in 1944 and again in 1949 revealed excellent function of the right kidney (fig. 3, *A* and *B*).

Case 4. A.H. No. 87448, S. G., a 53 year old white woman, was admitted to the urological service October 7, 1949, complaining of pain in the right kidney region following a fall 4 months before.

Excretory urograms elsewhere revealed a nonvisualization of the right kidney and normal left kidney.

She was treated conservatively for 4 months and when the pain in the right costovertebral angle persisted, she was referred for urological investigation.

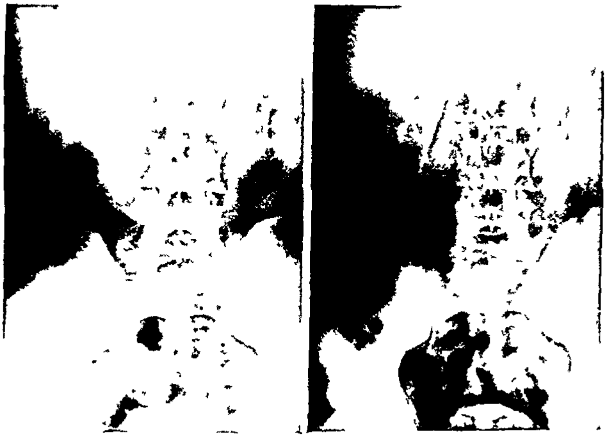

FIG. 3

She had lost 20 pounds since the onset of her illness. There were no other urinary symptoms.

On physical examination a moderately tender mass was palpated in the right kidney area.

There were 3 to 5 white blood cells per high power field in the urine. Moderate anemia was present. The right kidney was not visualized on excretory urography.

On cystoscopy, a No. 5 olive tip catheter became obstructed at 18 cm. up the right ureter. Ureterograms and stereoscopic studies revealed a marked degree of hydronephrosis of the right kidney with a dilated proximal segment of the ureter with medial and upward angulation of the upper ureter. The ureter then disappeared and reappeared lying medially over the vertebral column and then proceeded downward into the pelvis (fig. 2, *D*).

This typified the features of retrocaval ureter and after all studies had been completed a right lumbar exploration was performed. A large hydronephrotic kidney was found. The lower pole could not be readily mobilized. Nephrectomy was performed by freeing the upper pole, ligating the pedicle and then following the pelvis and dilated ureter down to its disappearance at the cava.

The ureter was observed to be markedly dilated proximally and to pass beneath the vena cava. The ureter was divided between clamps and the specimen removed. The wound was closed.

The patient made an uneventful recovery and was discharged on the twelfth postoperative day.

DISCUSSION

The increasing number of cases reported in the past decade, over that of the previous 40 years, and its characteristic features require a better understanding and appreciation of this urological entity.

Hydronephrosis has usually been ascribed to stricture, aberrant vessels, adhesions, etc., but in right hydronephrosis, vena caval impediment to drainage must be considered whenever there is a long proximal ureteral segment and the ureter lies on the vertebral column or beyond the midline.

With the correct preoperative diagnosis being made more often, consideration can be directed to the surgical repair which must be approached as the plastic surgeon should consider the problem; namely, the long term end result with avoidance of stricture and infection.

The most effective procedure seems to be Harrill's operation, where the pelvis is divided and it together with the proximal ureter is then anastomosed anteriorly to the cava. This avoids ureteral stricture, stone and infection.

The hazard of the latter is also made less likely with the use of antibiotics, ureteral splinting, pyelostomy drainage and better knowledge of plastic procedures.

Austen and Olsen have recently reported a case, the fortieth on record, the sixth case correctly diagnosed preoperatively, the eleventh where a plastic repair was attempted, and the ninth case where a successful result was obtained.

Eighteen cases have been clinical. Twenty-two cases have been in postmortem specimens.

We hereby add 4 cases, making the diagnosis in 2 preoperatively and using a successful plastic repair in one after Harrill's method. Follow-up studies 8 years later indicate a functioning kidney without infection. This is the longest follow-up on any case reported to date.

Another case had a nephrectomy and was diagnosed at surgery. One other case, in an adult male, was diagnosed radiologically. This patient refused surgery.

Inasmuch as cases in the human have been reported with retrocaval ureter and no hydronephrosis, we believe that this entity should be treated as any other congenital anomaly. It should be treated surgically only where definite obstruction, stasis, infection, hydronephrosis, etc., are present.

SUMMARY AND CONCLUSIONS

Retrocaval ureter is far more frequent than the total cases reported would indicate.

It should always be considered in right hydronephrosis where the proximal ureteral segment is long and dilated and the course of the ureter extends to the midline or beyond.

Roentgenology with opaque catheters and ureteropyelography offers the most precise method of diagnosis.

Four additional cases are added to the reported total of forty.

Three *cases were confirmed surgically. One was diagnosed on radiographic* grounds.

The preoperative diagnosis was established in 3 operative cases. Corrective plastic repair in 1 case has led to a functioning kidney followed now for 8 years, the longest follow-up to date.

75 Willett St., Albany, N. Y.

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CONGENITAL EXSTROPHY OF THE URINARY BLADDER: LATE RESULTS OF TREATMENT BY THE COFFEY-MAYO METHOD OF URETERO-INTESTINAL ANASTOMOSIS[1]

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"Statistically, 50 per cent of all persons afflicted with congenital exstrophy of the bladder are dead by their tenth year, and 66.6 per cent of them are dead by their twentieth year." These figures, quoted by C. H. Mayo in opening a discussion in 1925, have long been accepted in the prognosis for individuals born with an exstrophic urinary bladder.

In 1947 a patient who had undergone bilateral ureterosigmoidostomy and cystectomy for congenital exstrophy at the Mayo Clinic 35 years previously came under our observation. This patient had been the first to undergo such treatment at the clinic, and the second one of record to sustain ureteral transplantation along technical principles laid down by Coffey, the operation on the first having been performed by Middleton on March 1, 1911.

In the vast literature on this subject there is a conspicuous lack of studies relative to the long-term status of patients with an exstrophic urinary bladder and subsequently treated by uretero-intestinal diversion of the urinary stream. As our patient eventually came to nephrectomy, it was decided that investigation might reveal others whose subsequent course had necessitated surgical intervention. Too, such a study might reveal valuable information relating to morbidity arising as a direct result of ureteral transplantation, longevity, and general state of being of this group of patients. Accordingly, a questionnaire was sent to all patients who had undergone bilateral ureterosigmoidostomy at the Mayo Clinic from 1912 through 1946.

Congenital exstrophy of the urinary bladder has been defined as a malformation found in both sexes, in which the anterior wall of the bladder and that portion of the anterior abdominal wall over it are missing, so that the inner surface of the posterior wall of the bladder protrudes on the abdomen and the ureters expel urine externally. All patients in this series had deformities commensurate with this definition, and no attempt was made to classify them further.

The cause of exstrophy is unknown. Many theories have been advanced to explain its presence. Their very number readily attests the lack of fundamental knowledge in this respect.

It is a rare condition, being said to occur approximately once in every 40,000 births. Males, it is generally believed, are afflicted five times more frequently than females.

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[1] Abridgment of thesis submitted by Dr. Harvard to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology.

PRESENT STUDY

Out of more than 1,500,000 admissions to the clinic, 198 patients with congenital exstrophy of the urinary bladder were discovered. Of these, 144 were treated by uretero-intestinal diversion of the urinary stream, the majority (133 patients) by the Coffey-Mayo technique, with minor variations, as described in detail by Mayo and Hendricks. Moynihan's modification of Maydl's technique was employed in 1 case. In the remaining 10 cases simply one-stage operations using the Coffey-Mayo technique of transplantation were used.

The other 54 patients either refused surgical treatment or were treated by palliative operations because the presence of severe renal damage made ureterosigmoidostomy an unwise procedure.

In the entire group there were 134 males and 64 females, a ratio of approximately 2:1 in contrast to the usually quoted ratio of 5:1.

Of those undergoing operation, the youngest was 10 months and the oldest 49 years of age. The preponderance of patients operated upon fell in the first and third decades, with those in the former decade prevailing by 2:1. The patients were presented for examination at widely varying ages. Usually, however, if the patient was presented in infancy the parents were advised to return with the child when it had learned control of the bowel—usually around 3 or 4 years of age.

There are, perhaps, two reasons for the greatest numbers having been operated upon in the first and third decades. The first is that many parents sought to have the condition remedied as early as possible. Secondly, if they failed to do so for one reason or another during infancy or childhood, the adolescent child's approaching adulthood with its responsibilities demanded that something be done to render the child socially acceptable (fig. 1).

Of the original group of 144 patients who had undergone uretero-enteric anastomosis for exstrophy, 128 were definitely traced. The questionnaire sought information relative to the patients' general health, occurrence of pyelonephritis, and any further operations upon the urinary tract that might have been necessary. In the course of the investigation it was discovered that 2 patients had had nephrectomy elsewhere for stone. Unfortunately, the specimens in these cases were not available for study. In addition to the original patient, another of similar history, had had nephrectomy at the clinic. The specimen from a third patient who died elsewhere in uremia was made available to us. It consisted of the kidneys, ureters and contiguous portion of the sigmoid colon. These cases will be reported in detail. One other patient had had bilateral nephrostomies performed elsewhere for relief of bilateral hydronephrosis.

Postoperative mortality.—A total of 18 deaths occurred postoperatively in the entire series of 144 cases, that is, the deaths occurred before the patients left the hospital. Of this group, 7 patients died following the first stage of the two-stage operation, 7 died following the second stage of the two-stage operation, and 4 died following the one-stage operation. This gives an over-all mortality rate of 12.5 per cent (none died following cystectomy), or a rate of 10.5 per cent for the two-stage operation (table 1).

Hinman has collected from the literature reports of 124 cases in which the transplantation of the ureter for benign conditions was accomplished by application of the Coffey principle. The over-all surgical mortality rate in his series was 15.3 per cent, 19 deaths being reported.

It is of interest to note the marked difference in the surgical mortality rates between the one-stage and two-stage operations in the present study. Of the 4 deaths that followed the one-stage operation the first occurred in 1915 after ureteral transplantation by Moynihan's technique. The remaining 3 all occurred in 1926. The patients died of renal sepsis on the third, fifth and twentieth days respectively. No further one-stage operations were performed for exstrophy until 1943. There have been 5 such cases since 1943, in all of which the patients were living and well as of January 1, 1947.

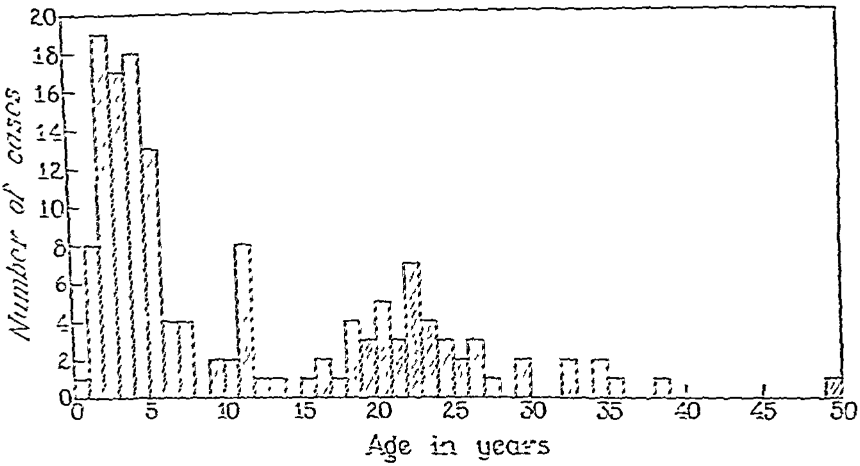

FIG. 1. Distribution of cases according to patient's age at time of operation

TABLE 1. *Hospital mortality rate according to type of operation*

OPERATIONS		HOSPITAL DEATHS	
Type	Number	Number	Per cent
One-stage	11	4	36.4
Two-stage	133	14	10.5
All types	144	18	12.5

The primary cause of postoperative deaths in this series of patients was overwhelmingly of renal origin (table 2).

Deaths after patients left the hospital.—The length of survival of the patients who died after leaving the hospital varied widely, the earliest death occurring 56 days after the patient left the hospital. Here, too, the deaths were preponderantly of renal origin (table 3).

Pyelonephritis.—The incidence of pyelonephritis in those surviving to January 1, 1947, as shown by their response to questions regarding chills, fever, backache, the necessity for medical attention, or further operation on the kidneys or ureters, is shown in table 4.

TABLE 2. *Hospital deaths according to cause*

CAUSE OF DEATH	PATIENTS	
	Number	Per cent
Pyelonephritis, ureteritis (with or without gangrene and peritonitis)	9	50.0
Generalized peritonitis	3	16.5
Pneumonia with or without empyema	2	11.1
Urinary extravasation	1	5.6
Massive retroperitoneal hemorrhage	1	5.6
Acute uremia secondary to inflammatory obstruction of ureteral orifices	1	5.6
Intestinal obstruction	1	5.6
Total	18	100.0

TABLE 3. *Deaths after the patients left the hospital*

CAUSE OF DEATH	PATIENTS	
	Number	Per cent
Uremia: pyelonephritis with stones or hydronephrosis or both	27	65.7
Undetermined	7	17.5
Ruptured appendix (necropsy)	1	2.4
Peritonitis of unknown origin	1	2.4
Influenzal meningitis	1	2.4
Pulmonary tuberculosis	1	2.4
Meningitis of unknown cause	1	2.4
Automobile accident	1	2.4
Suicide	1	2.4
Total	41	100.0

TABLE 4. *Incidence of pyelonephritis*

FREQUENCY OF ATTACK	PATIENTS	
	Number	Per cent
Denied symptoms—assumed not to have clinical pyelonephritis	21	30.4
Rare (once in several years)—controlled by chemotherapy	12	17.4
Occasional (0 to 1 time a year) to very frequent (every six weeks or oftener). Majority able to limit attacks to "a few days" by prompt use of sulfonamides or penicillin	36	52.2
Total	69	100.0

Urographic changes.—Of the 144 patients who had undergone operations, 41 had subsequent excretory urograms that were available for this study. The urograms represented a wide range in regard to postoperative time interval, 14 (34.1 per cent) being made during the first postoperative year, and 1 in the thirty-fifth postoperative year.

These urograms were studied for evidence of urinary obstruction manifested by ureteral or renal dilatation, nonvisualization, and the presence of stones (table 5).

The obstructive phenomenon of dilatation of the kidneys and ureters occurred with about equal frequency on the two sides. Nonvisualization, however, was noticeably predominant on the left, while stone formation was predominant on the right.

Five (12.2 per cent) of the excretory urograms were considered normal because they showed no evidence of obstructive phenomena above the site of anastomosis. One of these patients had been operated upon nineteen times prior to urography.

Carcinoma.—Of 198 patients with congenital exstrophy of the bladder, carcinoma of the bladder was discovered in 4. Three of these 4 patients underwent bilateral ureterosigmoidostomy. The fourth patient refused surgical treatment, and the ultimate cause of her death was unknown.

TABLE 5. *Obstructive phenomena shown by excretory urography (41 cases)*

	NO EVIDENCE OF DILATATION		DILATATION		NOT VISUALIZED		STONES	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Right kidney	16	39.0	20	48.8	2	4.9	3	7.3
Right ureter	13	31.7	23	56.1	2	4.9	0	0.0
Left kidney	12	29.3	21	51.2	8	19.5	1	2.4
Left ureter	10	24.4	23	56.1	8	19.5	0	0.0

The first patient, a woman 39 years of age with a grade 2 adenocarcinoma (graded on a basis of 1 to 4), lived 15 years following bilateral ureteral transplantation and cystectomy. She subsequently required a permanent left nephrostomy. The ultimate cause of her death was not determined.

The second patient, a man aged 36, with a grade 4 squamous cell epithelioma of the bladder, lived only 2 years after ureteral transplantation and cystectomy. He died elsewhere, but the circumstances of his death prompted his physician to state, tentatively, that he had metastasis to the brain. Necropsy was not performed.

The third patient, a woman aged 23, had a "papillary" carcinoma whose grade was not recorded. She lived 2 years following operation. The cause of her death was unknown.

The incidence of carcinoma of the bladder in this series is in accordance with generally held views as expressed by Graham, Abeshouse, and others.

Survival rates.—Of the total group of 144 patients, 106 had an opportunity to survive 5 years or more simply by virtue of having been operated on prior to

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Survival rates.—Of the total group of 144 patients, 106 had an opportunity to survive 5 years or more simply by virtue of having been operated on prior to

January 1, 1942. Of this group of 106 patients, 98 were definitely traced (either living or dead); 85 (86.7 per cent) of the 98 patients had survived five years or more. The other survival rates were arrived at in the same manner and are given in table 6.

The survival rates given in table 6 are shown graphically in figure 2, in comparison to the survival rates quoted by Mayo. They represent the nearest approach to true longevity figures following bilateral ureterosigmoidostomy for benign conditions to be published. Stevens in 1941 stated that "unfortunately, most results of operation are reported within a year, and later data are only rarely offered. Hence, true longevity figures are not available." He has been able to collect data on 28 patients who have survived 10 years or more following bilateral ureterosigmoidostomy for benign lesions. All save 1 of his patients had exstrophy. Eleven of the patients on whom he collected data had survived

TABLE 6. *Survival rates**

PERIOD	PATIENTS		LIVED BEYOND INDICATED PERIOD	
	Total	Traced	Number	Per cent of traced patients
years				
5	106	98	85	86.7
10	98	85	63	74.1
15	80	69	42	60.9
20	53	48	25	52.1
25	28	24	12	50.0
30	8	8	4	50.0

* Inquiry as of January 1, 1947. Included in the five-year group are only those patients operated on five or more years prior to the time of inquiry, that is, 1941 or earlier; and so forth.

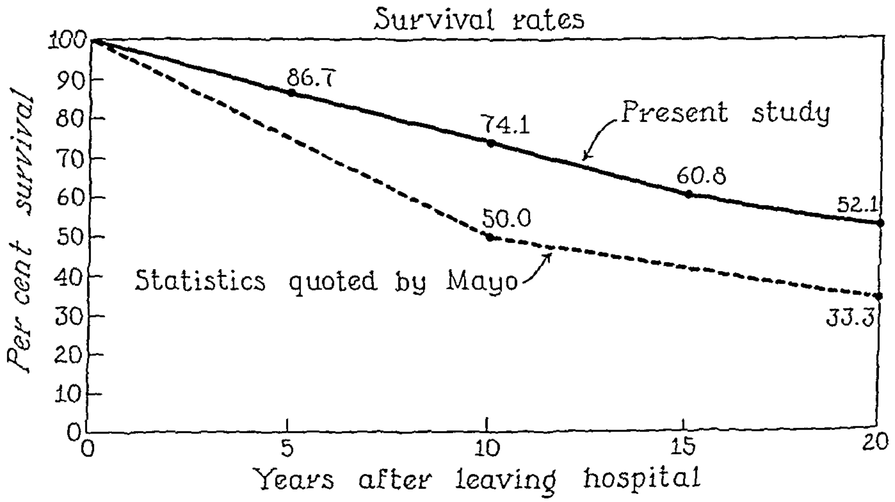

FIG. 2. Comparison of generally accepted survival rate of untreated patients (quoted by Mayo) with survival rate for those treated by the Coffey-Mayo method in our series.

more than 20 years, and 2 more than 30 years. He made no attempt, however, to establish survival rates.

The patient surviving longest in the present series has lived for 35 years following operation. Stevens refers to a patient who was operated on by Fowler in 1896; in 1941 that patient had survived for 43 years and 5 months. This, undoubtedly, is the longest reported survival.

If one may assume the survival rates as set forth in the opening paragraph of this paper to be correct, it is obvious that those patients having had their ureters transplanted have had their life expectancy increased by more than 20 per cent. A certain trend will be noted in this rate, namely, that the rate of survival decreases, roughly, 2 per cent per year for the first two decades.

In the entire series 4 patients had come to nephrectomy. Specimens from 2 of these patients were available for study. The urinary tract of a third patient who died elsewhere was made available to us.

REPORT OF CASES

Case 1.—A white boy 7 years of age was admitted to the Mayo Clinic on January 29, 1912. Physical examination revealed a healthy child except for exstrophy of the bladder and epispadias. On February 3, 1912, he underwent transperitoneal right ureterosigmoidostomy; on February 23, 1912, transperitoneal left ureterosigmoidostomy; and on March 12, 1912, extraperitoneal cystectomy. His convalescence was uneventful.

Nothing further was heard from the patient until 1921 when, in answer to a questionnaire, it was found that he suffered from intermittent chills, fever, and backache. He wore a pad during the day because he had not yet learned to control his bowels with confidence. His voiding interval was an hour and a half. The informant described him as being in good health and attending school.

On September 10, 1947, he was readmitted to the clinic complaining of chills, fever, pain in the left flank, malaise, and anorexia for the past week. Similar attacks had been recurring with increasing frequency over the past few years. During the intervening years he had been employed as a farm laborer. His bowel control was perfect, the voiding interval being four hours.

Physical examination revealed an acutely ill patient. The temperature was 101 F, the pulse rate was 84 per minute, and the blood pressure was 110 systolic and 74 diastolic, expressed in millimeters of mercury. There was tenderness to palpation over the left costovertebral angle and left upper abdominal quadrant.

Urinalysis disclosed a specific gravity of 1.012, albuminuria, grade 3, alkaline reaction, absence of sugar, and an occasional pus cell on microscopic examination. The blood contained 12.0 gm. of hemogloblin per 100 cc, the erythrocytes numbered 4,240,000, and the leukocytes 10,100 per cubic millimeter. The sedimentation rate (Westergren) was 106 mm. in one hour. The blood culture gave negative results. The blood urea measured 74 mg. per 100 cc and the creatinine content was 1.8 mg. per 100 cc. The excretory urogram revealed a nonfunctioning left kidney with probable stones, and a poorly functioning hydronephrotic right kidney.

A tentative diagnosis of calcareous pyonephrosis was established and nephrectomy was performed. The kidney was found to be hydronephrotic and full of stones. Microscopic examination disclosed widespread chronic inflammatory change throughout the cortex, and a diagnosis of chronic pyelonephritis of the obstructive type was made.

The postoperative course was uneventful. The value for blood urea remained elevated throughout the entire course and it was 66 mg. per 100 cc at the time of dismissal. Likewise the specific gravity of the urine remained fixed, the reaction remained alkaline, and albumin was constantly present. The values for serum protein and chlorides were within normal limits.

Case 2.—A white boy aged 3 years was admitted to the clinic on September 20, 1916. Physical examination revealed a normal healthy child except for an exstrophic bladder and a rudimentary penis and scrotum.

Transperitoneal right ureterosigmoidostomy was performed on September 27, 1916, the left ureter was similarly transplanted on October 14, 1916, and cystectomy was carried out on October 21, 1916. The postoperative course of each procedure was tranquil.

In 1930 information was received that the patient's general health was good; his voiding interval was 2 to 4 hours, but he frequently wet the bed at night. He had no symptoms suggesting renal infection. His genitalia had developed normally in size, and he was an active schoolboy indulging in such activities as tennis and swimming.

In 1939 his excretory urograms, made elsewhere, were reported to reveal a normal condition.

On December 24, 1946, he was readmitted to the clinic complaining of chills, fever, malaise, and acute pain in each costovertebral angle; these complaints had been present for several days. He had apparently been well until 1941 when he began to experience recurrent attacks similar to the present one, all of which responded well to sulfonamide drugs. In addition, he had passed bright red blood from the rectum on several occasions and had been told that he had a rectal polyp. His voiding interval was about 3 hours, with perfect continence.

On physical examination the temperature was 98.2 F, the pulse rate was 80, the respiration 20, and the blood pressure was 110 systolic and 60 diastolic. There was moderate tenderness in the left costovertebral angle and in the left testis. In addition, a ventral hernia was found at the site of cystectomy, and a small, hard mass was palpable on the left lateral wall of the rectum.

Urinalysis revealed a specific gravity of 1.019, grade 2, albuminuria, alkaline reaction, absence of sugar, and an occasional erythrocyte and an occasional pus cell. The blood urea measured 30 mg. and the blood chlorides 611 mg., the carbon dioxide combining power was 46 volumes per cent, the sedimentation rate was 81 mm., the hemoglobin measured 11.2 gm., the erythrocytes numbered 3,350,000 and the leukocyte count was 6,000.

In the excretory urogram the soft tissue outline suggested a fused kidney. On the right side the calyces and pelvis were normal except for rotation suggesting horseshoe deformity, and the ureter was normal. The left side was not visualized in any film.

Because of the history and the finding of an apparently nonfunctioning segment of a horseshoe kidney, exploration with a view to nephrectomy was performed. The kidney was found to be the horseshoe type, enlarged, and thickened with rather extensive inflammatory changes in the perirenal fat. The spermatic vessels crossed the ureter, producing partial obstruction.

Microscopic examination of the kidney showed evidence of an old, mild inflammation upon which had been superimposed acute pyelonephritis. This latter development had caused serious tubular damage, and a large number of tubules were filled with pus casts.

The postoperative course was uneventful. At the time of the patient's dismissal the laboratory findings were as follows: sedimentation rate 40 mm.; blood chlorides, 590 mg.; carbon dioxide combining power, 56 volumes per cent; and serum proteins, 7.2 gm. The urinary findings were unchanged.

Case 3.—A white man aged 21 years was admitted to the clinic December 2, 1926, complaining that his bladder had been "open" since birth, and that in the past 2 years partial fecal incontinence, particularly when riding horseback, had developed. Physical examination showed him to be of somewhat effeminate habitus, with an exstrophic bladder, complete epispadias, and bilateral inguinal hernias. Clear urine spurted from each ureteral orifice.

On December 20, 1926, a right transperitoneal ureterosigmoidostomy was performed. The surgeon noted that "the ureter was three times normal size" and that the operation was "unusually difficult." On December 31, 1926, the left ureter was transplanted and similar changes and difficulties were encountered. The postoperative course was uneventful.

Following extraperitoneal cystectomy on January 13, 1927, an abscess, which drained spontaneously after 2 weeks, developed in the left lower quadrant.

Nothing further was heard from this patient until June 10, 1938, when he was readmitted to the clinic with a history of recurrent attacks of chills and fever for the preceding 18 months. These responded well to urinary antiseptics. In the interim he felt well, was married, and followed an active farmer's life. His bowel control was good, and the voiding interval was satisfactory. Physical examination revealed a thin, pale man of effeminate habitus with temperature of 99.3 F, a blood pressure of 108 systolic and 74 diastolic, a pulse rate of 84 and a respiratory rate of 20. The testes were normal except that they were placed widely in lateral folds of skin representing a rudimentary scrotum.

The specific gravity of the urine was 1.018, albuminuria was graded 2, the reaction was alkaline, sugar was not present, and an occasional erythrocyte was observed on microscopic examination. The hemoglobin content of the blood was 13.1 gm., the erythrocyte count was 4,990,000, and the leukocyte count was 13,500. The blood urea measured 42 mg. The excretory urogram revealed bilateral nephrolithiasis, ureterectasis, and calyectasis.

A right pelviolithotomy was performed on June 15, 1938. The kidney was found to be in "pretty good condition except for a moderate degree of pyelectasis and calyectasis." Many small fragments of stone were removed. The postoperative course was uneventful.

The patient was re-examined on November 23, 1938, and found to be in good condition except for a small stone in the left kidney; this stone had been noted on the previous examination.

This patient died on January 10, 1948, in uremia. His physician reported that he had been well until a few months prior to death. At necropsy the kidneys, ureters, and contiguous portion of the sigmoid were preserved and made available to us. The kidneys were grossly dilated, the cortices being markedly thinned and scarred. The medullary portions were irregular and the pyramids were difficult to discern. A large, branched calculus was present in the right pelvis, and many small stones were noted in the left.

Upon examination of the uretero-intestinal anastomoses the opening of the right ureter was found to simulate the papilla of Vater and was easily patent. There was evidence of chronic inflammation at the site of the transplant, but apparently function was satisfactory. On the left side, a large, flat stone was lodged in the ureter at its junction with the colon. Apparently this stone offered only partial obstruction to the flow of urine, for the orifice was completely patent after the stone's removal. This orifice, too, resembled the papilla of Vater.

COMMENT

In viewing this study one must bear in mind the fact that the work reviewed is the product of many hands over many years. During these years chemotherapy has been radically improved and the antibiotics have been introduced. These last two obviously have not played a significant role in the operative mortality in this series, but undoubtedly will in any future series. Unquestionably they have contributed much to the lives and comfort of these patients. One notes that most postoperative deaths fall into a group that might well be labeled "infectious."

Let us consider, briefly, the lives of those who have undergone this treatment. They have been restored to society where formerly they were voluntary outcasts. If the patient is very young at the time of operation, the mental trauma of ostracism and of being an object of curosity and pity is minimized.

The operation does not necessarily preclude parenthood. Randall and Hardwick in 1934 were able to collect from the literature reports on 28 women on whom bilateral ureterosigmoidostomy had been performed and who subsequently were delivered of children. Five of those were included in our study. One of the 5 was the mother of twins; one had 3 children, while the others each had a single child. Of great interest is the fact that only 1 of these patients during any pregnancy exhibited signs of urinary infection. Two of these women were grandmothers.

Fatherhood is not beyond question although we have no record of its having occurred as the result of coitus. Many of the men with congenital exstrophy are able to have plastic reconstruction of the penis and subsequently perform normal coitus. Usually following such reconstruction the ejaculatory ducts open on the skin surface of the peno-abdominal angle, the semen being dissipated upon ejaculation. However, we have on record in this series 1 instance of fatherhood in which 1 such patient acted as donor for the artificial insemination of his wife.

The bowel habit of these patients is, in general, good. If they have been continent of feces prior to operation, one may expect that they will be continent of urine as well. After varying periods of time—usually a matter of weeks—they begin to develop differential bowel function and are able to defecate and urinate separately.

The range of activities of these patients varies widely. Our records show that by and large school children are active, participating in such normal childhood pursuits as swimming, baseball, tennis, riding and the like. The adults pursue careers that range from day labor—one is a circus roustabout—to the professional fields. In the majority of instances the patients do not seem to have been crippled or handicapped severely by the recurrence of pyelonephritis. One cannot help feeling that use of the newer chemotherapeutic and antibiotic agents is going to enhance the lot of such patients immeasurably, particularly in that group in which pyelonephritis has caused chronic invalidism and death.

SUMMARY AND CONCLUSIONS

The final answer to the problem of surgical treatment of congenital exstrophy of the bladder has yet to be written. The writing of scores of surgeons and the wide variety of techniques employed during the past century readily attest to this fact. Our study does not attempt to give the answer, but merely reviews the late results obtained with the Coffey-Mayo technique as one of the many surgical approaches to the problem.

One hundred and ninety-eight patients in more than 1,500,000 admissions to the Mayo Clinic were found to have exstrophy of the bladder. One hundred and forty-four of these were treated by uretero-intestinal anastomosis.

Males predominated over females 2:1. The ages of those undergoing operation varied from 10 months to 49 years, with most patients undergoing operation in the first and third decades.

The postoperative mortality rate was 10.5 per cent for the 133 patients who underwent the two-stage operation. Well over 60 per cent of the total number of postoperative deaths (18 deaths) were of renal origin. Sixty-five per cent of the deaths that occurred after the patient left the hospital were ascribed to renal failure.

A little more than two thirds of 69 patients who survived operation and were living on January 1, 1947, gave more or less evidence of having pyelonephritis.

In 41 postoperative excretory urograms dilatation of the kidneys and ureters was about equally common on the two sides. Nonvisualization was more common on the left side, while stones were encountered more often on the right.

Four of 198 patients had carcinoma of the exstrophic bladder.

Eighty-five of 98 traced patients on whom operations had been performed had survived for five years or more.

One may conclude from this study that while transplantation of the ureters to the bowel is not a perfect operation in the physiologic sense, it does offer a great measure of relief from an otherwise very distressing situation. It has shown that the life expectancy of persons with an exstrophic bladder is increased measurably by suitable treatment and that their subsequent lives may be nearly normal. It has shown that the major problem in the subsequent treatment of such patients is the control of pyelonephritis, and that the pyelonephritis is most frequently accompanied by obstructive phenomena. The advent of the newer chemotherapeutic agents and antibiotics may do much to reduce the disability thus incurred, but it will not answer the whole problem.

REFERENCES

Abeshouse, B. S.: Exstrophy of the bladder complicated by adenocarcinoma of the bladder and renal calculi: A report of a case and a review of literature. J. Urol., **49:** 259, 1943.

Coffey, R. C.: Pancreato-enterostomy and pancreatectomy. Ann. Surg., **50:** 1238, 1909.

Coffey, R. C.: Physiologic implantation of the severed ureter or common bile-ducts into the intestine. J.A.M.A., **56:** 397, 1911.

Fisher, J. H.: A case of ureteral transplantation (Peters' operation) surviving twenty-two years. Brit. J. Urol., **10:** 241, 1938.

Graham, W. H.: Ectopia vesicae complicated by adenocarcinoma, with a review of the literature. Brit. J. Surg., **30:** 23, 1942.

Higgins, C. C.: Transplantation of the ureters into the rectosigmoid in infants. Tr. Am. A. Genito-Urin. Surg., **36:** 267, 1943.

Hinman, F.: The Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1935, p. 420.

Hinman, F. and Weyrauch, H. M., Jr.: A critical study of the different principles of surgery which have been used in uretero-intestinal implantation. Tr. Am. A. Genito-Urin. Surg., **29:** 15, 1936.

Lower, W. E.: Late results following transplantation of ureters into the rectosigmoid. Tr. Am. A. Genito-Urin. Surg., **36:** 279, 1943.

Maydl, K.: Ueber die radikaltherapie der Ectopia vesicae urinae. Wien. med. Wchnschr., **44:** 1113; 1169; 1209; 1256; 1297, 1894.

Mayo, C. H.: Exclusion of the bladder, an operation of necessity and expediency. Ann. Surg., **58:** 133, 1913.

Mayo, C. H.: Exstrophy of the bladder and its treatment. J.A.M.A., **69:** 2079, 1917.

Mayo, C. H.: Methods of ureteral repair and transplantation. Ann. Surg., **82:** 472, 1925.

Mayo, C. H. and Walters, W.: Transplantation of the ureters into the rectum: End results in 35 cases of exstrophy of the bladder. J.A.M.A., **82:** 624, 1924.

Mayo, C. H. and Hendricks, W. A.: Exstrophy of the bladder. Surg., Gynec. & Obst., **43:** 129, 1926.

Middleton, G. W.: Submucous ureteral implantation into the bowel: Twenty year report on the first human case. J.A.M.A., **97:** 1536, 1931.

Moynihan, B. G. A.: Extroversion of the bladder: Relief by transplantation of the bladder into the rectum. Ann. Surg., **43:** 237, 1906.

Randall, L. M. and Hardwick, R. S.: Pregnancy and parturition following bilateral ureteral transplantation for congenital exstrophy of the bladder. Surg., Gynec. & Obst., **58:** 1018, 1934.

Stevens, A. R.: Longevity following uretero-intestinal anastomosis, with report of cases. J. Urol., **46:** 57, 1941.

Wuitsch, M.: Ein Fall einer vor 40 Jahren operierten, beschwerdefrien, Harnblasenektopie. Wien. klin. Wchnschr., **58:** 325, 1946.

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COMPLETE CESSATION OF PERSISTENT BLADDER PAPILLOMATOSIS FOLLOWING NEPHO-URETERECTOMY AND SEGMENTAL CYSTECTOMY FOR PRIMARY PAPILLARY CARCINOMA OF URETER

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The case to be presented is of interest not only because the patient has been well more than 10 years after a right nephro-ureterectomy and segmental cystectomy for primary papillary carcinoma of the ureter but also because it suggests the possibility of a direct relationship between the removal of the kidney and the ureter and the complete cessation of recurrent bladder papillomas that were persistently present and most troublesome over a period of at least 26 months prior to the operation. When this case was first presented in 1943, as part of a review of primary carcinoma of the ureter, special emphasis was placed on those findings that seemed essential of assuring its acceptance as a proven and properly treated case of this character; and because we did not then attach any significance to the cessation of bladder papillomatosis following operation, that particular phase of the patient's problem was glossed over rather lightly, all too lightly, we now believe.

CASE REPORT

H. M., S. M. H., No. 139756, aged 52, was first seen April 23, 1938 because of recurrent attacks of hematuria. Following the first attack which occurred in August 1937, a diagnosis of chronic prostatitis complicated by hematuria was made elsewhere and a course of prostatic massage was given with no effect upon the hematuria. On cystoscopic examination, three pedunculated bladder tumors were seen, the largest of which was attached by a rather broad pedicle close to the right edge of the trigone and about 2 cm. inside of the vesical neck in the region of 8 o'clock. It was about 3.5 cm. in its greatest diameter; its surface which was necrotic in the center and covered by many short, fused, red papillae on its outer border, dropped into the vesical neck from about 7 to 10 o'clock. The cystoscopic impression of an early papillary carcinoma was confirmed by histopathological studies. A second but smaller tumor of the same pathological character was attached just above and a little medial to the right ureteral orifice and covered the upper tip of the trigone. There also was a smaller and more benign-appearing tumor located in back of the interureteric ridge, just a little to the right of midline (fig. 1). This tumor was easily destroyed by fulguration. The two larger tumors were successfully treated by endovesical radium and fulguration. During the next 10 months, the patient was cystoscoped four different times and on each occasion several small benign papillary tumors of the bladder were found and destroyed by fulguration.

This investigation was supported with funds from the Dr. Henry C. Buswell Memorial.

On September 11, 1939 he again returned because of hematuria and at this time complained of mild pain in right kidney region. On cystoscopic examination no bladder tumor was found and there was no bleeding from either ureter. Wax-tipped bougies were passed to each kidney and no hang or stone-scratch obtained. The urine from the right side contained a few white blood cells and

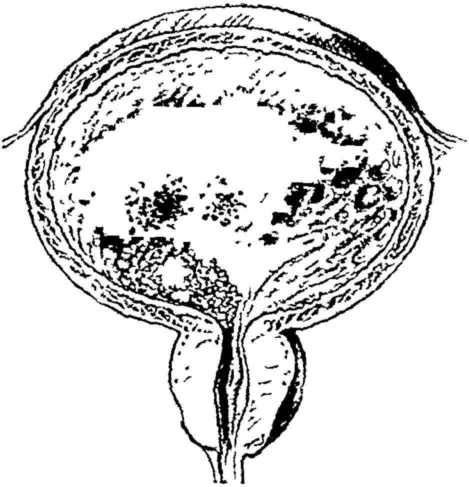

FIG. 1. Bladder tumors present on first examination; larger ones were papillary carcinomas.

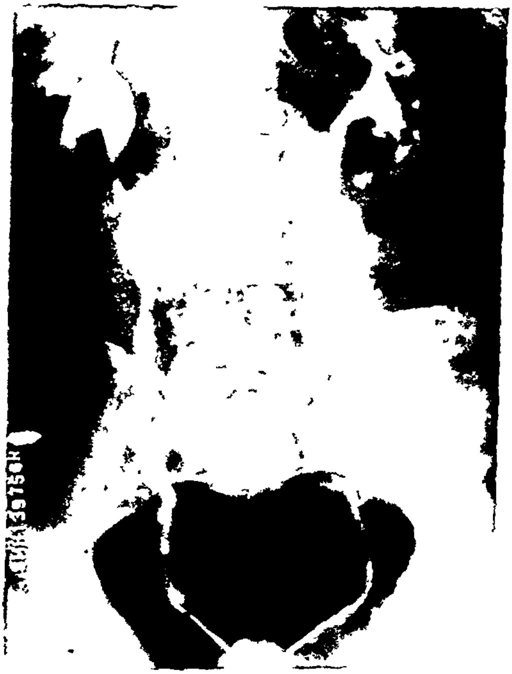

FIG. 2. Characteristic goblet-shaped filling defect in lower right ureter and moderate dilatation of ureter above suggested presence of pedunculated papillary tumor

bacilli. The phthalein appeared on the right side in 3½ minutes and on the left in 3 minutes and the output for 30 minutes was 22 per cent on the right and 17 per cent on the left. Stereoscopic retrograde pyelo-ureterograms were normal on

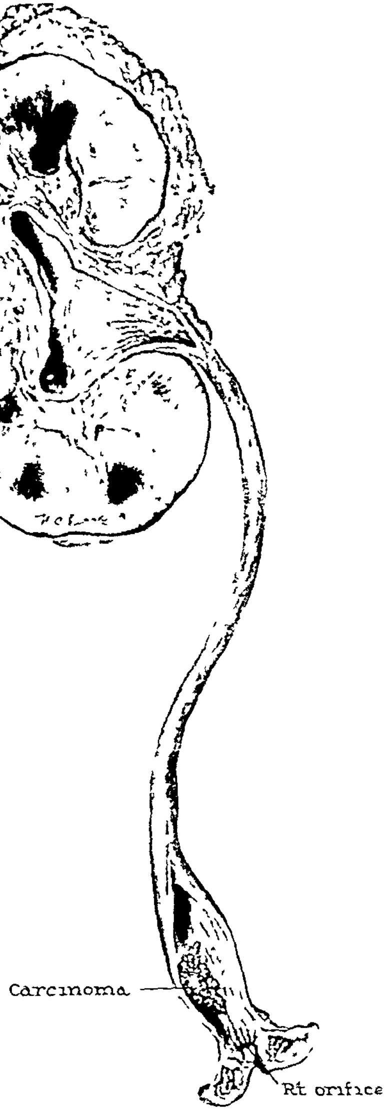

FIG. 3. Surface of tumor which was relatively much larger than its pedicle was covered by papillae, especially in central portion, that were short and fused. Ureter was dilated above and below tumor.

the left side but on the right there was a goblet-shaped filling defect in the lower end of the ureter with definite dilatation of the ureter above and a moderate dilatation of the renal pelvis (fig. 2). A diagnosis of tumor of the lower end of the ureter was made and operation advised. The patient procrastinated a time and it was not until October 9, 1939 that a nephro-ureterectomy and segmental cystectomy was performed. About 3 cm. above the ureterovesical junction what appeared to be a small, early, pedunculated papillary carcinoma was found. The ureter was definitely dilated above and below the tumor (fig. 3). Inasmuch as the gross and microscopic pathology of this tumor have been presented in detail in the previous report, it is sufficient to state at this time that the clinical impression of early papillary carcinoma of the ureter was confirmed by microscopic studies. Aside from a mild thrombophlebitis which occurred 23 days after operation and caused moderate edema of the left leg, the patient's convalescence was very satisfactory.

Three months after operation and 4 months after his last cystoscopic examination the bladder was examined again. At the site of the bladder resection there was a small area of edema or the early elevation of the bladder mucosa that sometimes precedes the appearance of a papillary growth; the examiner could not tell which, but did not attach enough significance to its presence to take sections for study. This area was lightly fulgurated. At this time the patient still had a marked Escherichia coli infection of the bladder. During the 10 years that have elapsed since operation the patient has submitted to routine cystoscopic examinations and aside from the area described above, nothing suggesting a recurrent or new growth of the bladder has been found. When last cystoscoped on March 3, 1949, his bladder mucosa was normal and his urine was uninfected. On November 28, 1949 the patient reported that he was feeling well, and his urine was sparkling clear.

DISCUSSION

In reviewing the literature on primary carcinomas of the ureter in 1943, we were able to find 183 acceptable cases to which we added 2 more. The fact that of the 32 patients who were reported as living, only 6 had been followed more than 4 years suggested the need of further follow-up information before the results of surgical treatment could be correctly evaluated. It was while reviewing this case with the thought of reporting it as an apparently satisfactory operative result that we first became impressed by the fact that this patient who had been a victim of persistent papillomatosis of the bladder for a period of at least 26 months prior to the nephro-ureterectomy and segmental cystectomy had subsequently been completely free from further trouble of this sort for more than 10 years. To us, this observation seemed significant and worthy of further consideration.

There are a number of reasons why the growths were in all probability not implants to the bladder from the tumor in the lower end of the right ureter and therefore ceased to occur following its removal. Two of the 3 tumors found in the bladder at the time of the first cystoscopy, 17 months prior to the discovery of the small tumor in the ureter, were relatively large, mature-appearing, papillary carcinomas. The patient's first symptoms pointing toward a possible kidney or ureteral lesion were present but a few days before the lesion was discovered; and the tumor, which was small, had only started to extend into the deeper structures of the ureter at its base. The ureter and kidney above the tumor were not greatly dilated as in the case of obstruction of long duration and the renal function of this kidney was even a little better than that of its normal-appearing mate on the opposite side. Finally the patient is alive and apparently well more than 10 years after operation suggesting early discovery and correction; as metastases usually occurs early in this disease.

But there are other clinical and experimental findings that indicate that the appearance of the tumor in the right ureter was a rather late link in the chain of events that had been occurring for at least 26 months and probably longer prior to its discovery. It is well known that workers in certain dye industries may be exposed to drugs possessing proven carcinogenic properties for months and even years before bladder papillomas begin to appear and that these growths are more frequently found in the base of the bladder where the urine tends to puddle resulting in a more constant action of the etiological factor. Hueper, et al. in their experimental production of bladder tumors in dogs, using beta-naphthylamine as the carcinogenic agent observed that the precursor and tumor lesions had a marked tendency to appear in the most dependent portion of the animals' bladder; namely the distal two thirds of the anterior wall, a little less of the lateral walls and the upper two thirds of the posterior wall. Macalpine reported 2 cases of papillary tumors of the renal pelvis occuring in dye workers in which the renal tumor was discovered in one, 3 years and the other 5 years after the onset of bladder papillomatosis. In both instances he thought the growths in each organ were primary tumors. Furthermore he observed that while bladder tumors were not uncommon in dye workers, renal tumors were relatively rare; he was only able to find 6 cases to which he added 2 more.

If we were to concede the possibility that this patient's bladder papillomatosis could be due to the action of some unknown carcinogenic agent, we could find nothing in his history to suggest that it was exogenous in origin. A careful check of his habits, activities and environment prior to his operation revealed nothing of significance and since then there has been little or no change in any of these. As a result of experimental work on rabbits by Rous, Beard and Kidd and the clinical observations by Kirwin, a virus infection has been introduced as the possible etiological factor in cases of this sort but its presence in humans, at least, has never been demonstrated.

It would therefore seem more likely that the carcinogenic factor in this case, whatever it may have been, was endogenous in origin, and may have been related to or at least it may have possessed some of the characteristics of the extracts used by Steiner, Stanger, and Bolyard in their very interesting work on this subject. The fact that the majority of the benign and malignant papillomas of the bladder occur in patients between 40 and 59 years of age and the observations by Haddow, Watkinson and Patterson, as well as those of Lich and Grant, on the effects of estrogenic therapy on these tumors suggest that their appearance may be closely influenced by the metabolic and endocrine changes that occur at that time of life. If this were the case, one would expect that bilateral renal and ureteral papillary tumors would occur practically as commonly as unilateral involvements, but actually, such findings are very rare. It would therefore seem that either as the result of some general systemic force or a physiological functional change within itself the filtration threshold of but one of the kidneys, at first, is altered to the extent that the activating agent is permitted to pass into the urinary stream. The complete cessation of persistent bladder papillomatosis of long duration after a nephro-ureterectomy and segmental cystectomy for primary papillary carcinoma of the ureter that had apparently been present but a short time suggests the possibility of but a unilateral excretion of the carcinogenic agent in this case.

CONCLUSIONS

A case in which the patient is apparently well and free from tumor more than 10 years after a right nephro-ureterectomy and segmental cystectomy for a primary carcinoma of the ureter has been presented.

The complete cessation of persistent bladder papillomatosis of 26 months' duration following the operation suggests that the etiological factor arrived at the bladder by way of the right kidney alone.

REFERENCES

HADDOW, A., WATKINSON, J. W. AND PATTERSON, E.: Brit. M. J., **2**: 392, 1944.
HUEPER, W. C., WILEY, F. H., WOLF, H. D., RANTA, K. K., LEMING, M. F. AND BLOOD, F. R.: J. Indust. Hyg., **20**: 46, 1938.
KIRWIN, T. J.: J. Urol., **49**: 1, 1943.
LICH, R., Jr., AND GRANT, O.: J. Urol., **59**: 682, 1948.
MACALPINE, J. B.: Brit. J. Surg., **35**: 137, 1949.
ROUS, P., BEARD, J. W., AND KIDD, J. G.: J. Exper. Med., **64**: 401, 1936.
SCOTT, W. W.: J. Urol., **50**: 49, 1943.
SCOTT, W. W. AND MCKAY, R. W.: New York State J. Med., **27**: 939, 1927.
STEINER, P. E., STANGER, D. W. AND BOLYARD, M. N.: Cancer Res., **7**: 273, 1947.

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THE ABSORPTION OF CERTAIN CONSTITUENTS OF URINE FROM THE LARGE BOWEL OF THE EXPERIMENTAL ANIMAL (DOG)

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Diversion of the entire urinary stream of the experimental animal (dog) to any part of the small intestine from the duodenum to the lower ileum is incompatible with life. Transplantation of one ureter to the small intestine results in no significant change in the blood levels of nonprotein nitrogen, urea nitrogen, or creatinine providing the opposite kidney remains functionally normal and urine is disposed of through the usual channels.

Clinical and experimental results have established proof that the diversion of the entire urinary stream to the sigmoid colon and rectum permits survival of the animal for indefinite periods. The absorption of nitrogenous constituents of urine from the colon has not been definitely established. Sauer in a recent review of clinical material has reported a frequent transient increase in blood nonprotein nitrogen following ureterosigmoidostomy of types other than the Coffey No. II, in which urine is temporarily drained outside the bowel by ureteral catheters. The author has noted that prompt reduction of elevated blood nonprotein nitrogen of the patient with ureterosigmoidostomy will frequently follow the institution of constant rectal drainage.

There has been no published account of an effort to determine the degree of reabsorption of the constituents of urine from the cecum and the transverse and descending colon. Such an investigation seemed warranted in view of recent reports of the transplantation of one ureter to the cecum, either for convenience to the surgeon or because the surgery has been so extensive as to eliminate the distal portion of the colon.

MATERIALS

A total of 38 dogs were used in these experiments. Unselected adult animals ranging in weight from 20 to 50 pounds were taken from the stock pen. These animals were observed for a period of 7 to 14 days prior to operation. During this time they were de-barked and were immunized against rabies and distemper. Two or more fasting blood samples were taken from the external jugular vein at intervals of 3 days. A base line of normal values was thus established for the following: blood nonprotein nitrogen, blood urea nitrogen, blood creatinine, blood uric acid, serum inorganic phosphorus, serum carbon dioxide combining power, and whole blood chlorides.

METHODS

The animals were divided into two major groups. Operations were performed alternately on animals from group 1 and from group 2.

Read at annual meeting, American Urological Association, Washington, D. C., May 30, 1950.

Dr. Boyce's manuscript was awarded first prize by the Committee on Scientific Research, Dr. Miley B. Wesson, chairman. *Editor.*

Group 1. Fifteen animals comprised this group. In all of these animals the urethra was ligated and divided and the dome of the bladder anastomosed to the cecum (figs. 1 and 3). In 5 animals an ileostomy was performed simultaneously. The ileum was divided 5 cm. from its termination; the distal stump was ligated and inverted; the proximal end was brought out through the flank to form an ileostomy (fig. 6).

Group 2. Eighteen animals comprised this group. In all of these animals the urethra was ligated and divided and the dome of the bladder anastomosed to the midportion of the sigmoid colon (figs. 1 and 8). In 8 animals the colon was divided at the junction of the descending and sigmoid colon. The sigmoid stump was ligated and inverted. The descending colon was brought out through the wall of the left lower abdomen to form a colostomy (fig. 12). In 5 animals this procedure was done at the same time as the vesicosigmoid anastomosis. In 3 animals the vesicosigmoid anastomosis was done in one stage and the colostomy was done in a second stage 5 to 12 days later.

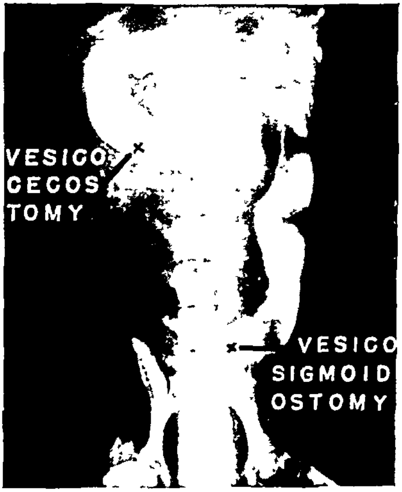


FIG. 1. Diodrast enema of colon of normal dog. Labels indicate points at which anastomoses were made.

Five control animals were operated upon, 2 in a manner analogous to group 1 and 3 as in group 2. All stages of the operation were carried out, including incisions into the colon and bladder, but without completing the anastomosis.

There was no preoperative preparation of the animals other than the withholding of all food and water for 24 hours. A soapsuds and tap water enema was given immediately prior to operation.

Intravenous sodium pentabarbitol anesthesia 0.032 gm. per kg. of body weight was found to be satisfactory.

Strict attention to every detail of aseptic technique was maintained. A midline suprapubic incision was utilized to expose the abdominal cavity. The urethra was isolated and divided 1 to 2 cm. from the vesical orifice. In the male animal this was immediately proximal to the prostate. The distal stump of the urethra was doubly ligated and allowed to retract. The proximal stump was ligated with chromic catgut and inverted into the bladder through a silk purse-string suture.

The mobilization of the bladder permitted by division of the urethra and the mobilization of the cecum by division of the avascular portion of its mesentery resulted in approximation of these structures with little tension. The dome of the bladder was then anastomosed either to the cecum or to the sigmoid colon. The length of the anastomosis corresponded to the entire width of the dome of the contracted bladder (2.5 to 3.5 cm.). The cuff of bladder wall surrounding the anastomosis was 1 to 2 cm. in width. A soft rubber tube 6 to 8 mm. in diameter was left anchored through the anastomosis by a single suture. This step assured patency of the anastomosis during the early stages of healing. Coprostasis was effected by rubber bands placed about the colon above and below the point of anastomosis. Size 000 Deknatel silk sutures were used throughout the procedure. The abdominal wall was closed in layers without drainage.

During the operation and immediately afterward the animals received 20 cc per pound of body weight of intravenous fluids, two thirds of which was 5 per cent dextrose in water and one third normal saline. In the postoperative period intravenous fluids were given each 24 hours until the animal was taking adequate quantities by mouth. Such supplemental fluid intake was rarely necessary for more than 24 to 48 hours.

The animals were rotated through metabolism cages for 24-hour periods and the urinary output recorded 2 to 3 times weekly.

All animals were kept on an exactly similar diet of prepared dog biscuits supplemented by whole milk and a daily portion of fresh ground meat. No effort was made to prolong the life of the animals by high carbohydrate diets or the use of desoxycorticosterone acetate or testosterone.

Blood samples were taken from the external jugular vein 2 or more times during the preoperative period of observation and again on the day of operation. The average value of these determinations was taken as the normal, and all values listed on the day of operation ("0" day) on the accompanying charts represent such average values.

In the postoperative period blood samples were drawn from the external jugular vein at intervals of 24 to 72 hours. Blood nonprotein nitrogen determinations were made by the micro-Kjeldahl technique of Koch and McMeekin. Blood urea nitrogen was determined by the Gentzkow method. The standard Folin-Wu procedure was used for blood creatinine studies. Uric acid determinations were made on oxalated blood after the method of Folin. The method of Fiske and SubbaRow was used for colorimetric determination of serum inorganic phosphorus. Serum carbon dioxide combining power was done by the Van Slyke and Cullen procedure without modification. Samples were drawn into an oil coated syringe and kept under paraffin oil until analysis 1 to 2 hours later. Whole blood chlorides were determined by the method of Schales and Schales. Whole blood was used to avoid variations in plasma chlorides due to intracellular shift of the chloride ion.

Excretory urograms with diodrast 0.4 cc per pound body weight were done on the third to the fifth postoperative day and repeated in 2 to 8 weeks.

Autopsy was performed within a few hours of death in every instance. The examination was complete with the exception of the head. Microscopic sections were made from each kidney, the renal pelves, ureters, various levels of the gastrointestinal tract and occasionally from the bladder and pericardium. The kidneys were weighed after removal of all fat and vessels at the hilum and division of the ureter at the ureteropelvic junction.

OBSERVATIONS

Eight animals operated upon during the course of this experiment were omitted from the calculations and from the reported total of 38 animals because of complications which might have affected the concentration of the nonprotein nitrogenous constituents of the blood. These complications were: 2 instances of respiratory tract infection, 2 cases of subcutaneous wound infection, 2 cases of localized peritonitis, 1 instance of adhesions between loops of small intestine which may have caused partial intestinal obstruction, and 1 case of generalized peritonitis following disruption of a suture line.

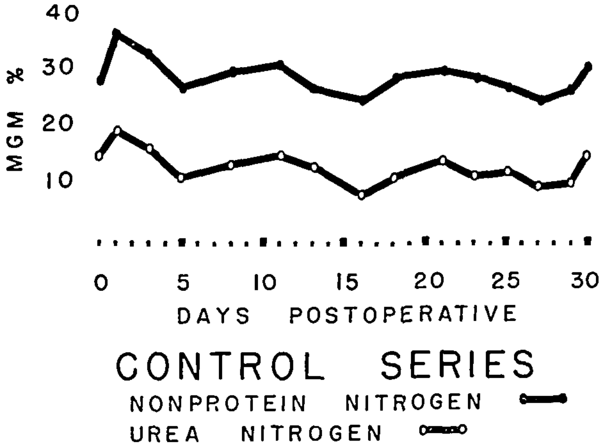


FIG. 2. Control series of 5 animals subjected to all stages of vesicocolic anastomosis excepting completion of anastomosis. Operation was done on "O" day. Values for blood nonprotein nitrogen and urea nitrogen are based on average figures for group.

Biochemical examinations revealed the following average preoperative values for the entire group of 38 animals: Blood nonprotein nitrogen 31.6 mg. per 100 cc (range 27 to 35); blood urea nitrogen 14.8 mg. per 100 cc (range 8 to 18); blood creatinine 1.5 mg. per 100 cc (range 0.8 to 2.4); blood uric acid 2.2 mg. per 100 cc (range 1.5 to 3.5); serum inorganic phosphorus 2.8 mg. per 100 cc (range 2.0 to 4.3); serum carbon dioxide combining power 49 volumes per 100 cc (range 45 to 56); whole blood chlorides 560 mg. per 100 cc (range 510 to 620).

Control series. The 5 control animals recovered promptly from the operation and appeared entirely healthy throughout the 30-day period of observation. The average change in blood urea nitrogen and blood nonprotein nitrogen is shown in figure 2. The maximum elevation in nonprotein nitrogen for any individual was 40 mg. per 100 cc on the second postoperative day. In every instance the nonprotein nitrogen and blood urea nitrogen returned to normal limits before the fifth postoperative day. The blood creatinine, blood uric acid, serum inorganic phosphorus, serum carbon dioxide combining power, and whole blood chlorides all remained within normal limits throughout the period of observation. Post-mortem examination revealed no gross abnormality of the gastro-intestinal tract or of the genito-urinary system. The average weight of the total renal tissue was 55 gm. with a range of 48 to 63 gm.

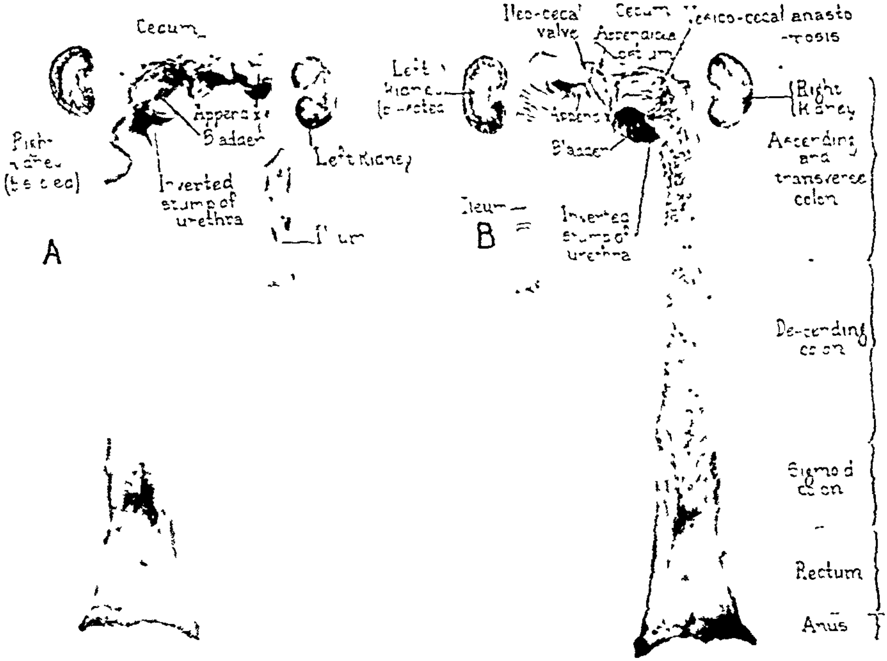


FIG 3 Vesicocecostomy Dog No 22, nineteen days postoperative *A*, ventral view *B*, dorsal view Bowel has been opened along line of mesentery. Ventral half of right kidney and dorsal half of left kidney have been removed

Group 1. Vesicocecostomy. All animals in group 1 expired in 15 to 24 days postoperative. The clinical course was characterized by the excellent general appearance of the animal until 24 to 72 hours prior to death. Appetite and oral intake of water were increased from the preoperative period. The preoperative urinary output of 60 to 110 cc per 24 hours for this group was increased to an average of 470 cc per 24 hours, with a range of 160 to 940 cc per 24 hours. The animals were alert and playful in the exercise yard. The first clinical change noted was weakness in climbing onto the shelves in the pen. This was accompanied by dryness and loss of elasticity in the skin so marked as to suggest severe dehydration. Lethargy, refusal of food and water followed in rapid succession. The muscular incoordination became rapidly more severe so that the animal was unable to stand and weaved drunkenly when supported. Coma and death occurred 24 to 72 hours after onset of the first symptoms. Vomiting was so rare as to be observed in only one animal. Terminal muscle twitching was not observed in any animal in the series.

The blood nonprotein nitrogen of group 1 exhibited a prompt and sustained elevation (fig. 4). In 8 individuals the concentrations were remarkably parallel, increasing progressively to an average of 106 mg. per 100 cc 24 to 36 hours before death (fig. 4, *B*). Two animals, Nos. 6 and 7 in figure 4, *A*, exhibited an appreciable deviation from the other members of the group in the more rapid increase in the blood nonprotein nitrogen and greater elevation at the time of death (154 and 168 mg. per 100 cc, respectively).

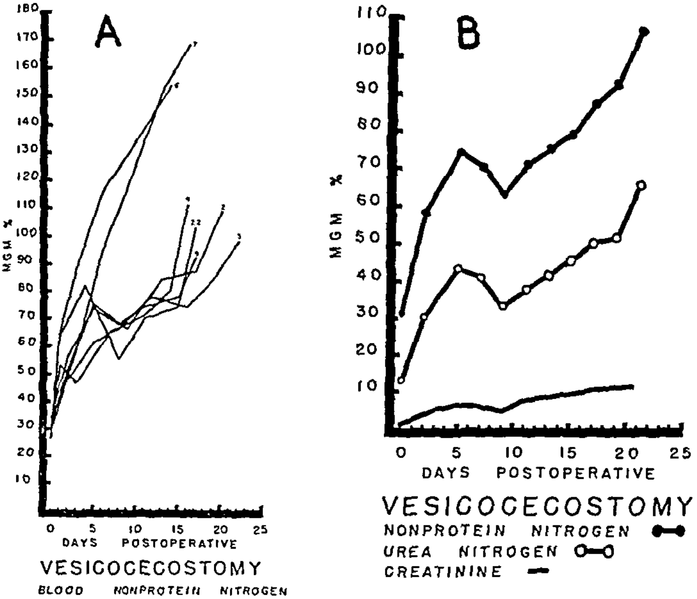


Fig. 4. *A*, vesicocecostomy. Individual variations in blood nonprotein nitrogen. Small figures indicate number of experiment. For clarity not all individuals nor all determinations of any one individual are present. Range of extreme variation is represented. Death occurred 24 to 72 hours after last recorded determination. *B*, vesicocecostomy. Average variations of blood nonprotein nitrogen, urea nitrogen and creatinine in 8 animals. Animals Nos. 6 and 7 (fig. 4, *A*) are not included.

The blood urea nitrogen was progressively increased (fig. 4, *B*). The average values of the blood urea nitrogen were approximately one half of the corresponding values for the total nonprotein nitrogen. However, fluctuation in the urea nitrogen was much more marked and unpredictable than figure 4, *B* would indicate. Individual determinations of urea nitrogen usually deviated from the recorded average by more than twice as much as the corresponding nonprotein nitrogen. A blood urea nitrogen concentration of 25 to 66 per cent of the total nonprotein nitrogen was not infrequent.

Creatinine was progressively elevated to an average blood concentration of 11 mg. per 100 cc just prior to death (fig. 4, *B*).

Blood uric acid concentration was immediately depressed to an average of 0.3 mg. per 100 cc on the sixth postoperative day and remained at approximately 0.5 mg. per 100 cc until just prior to death (fig. 5, *A*).

Serum inorganic phosphorus levels remained within the preoperative limits, varying from 2.8 to 4.4 mg. per 100 cc (fig. 5, *A*).

The serum carbon dioxide combining power was depressed to an average value of 30 volumes per 100 cc on the third postoperative day, and remained between 35 and 40 volumes per 100 cc until 24 to 48 hours before death (fig. 5, *A*).

Whole blood chloride concentration was increased from a preoperative average of 538 mg. per 100 cc to an average of 650 mg. per 100 cc (maximum 668 mg. per 100 cc) on the third postoperative day. Subsequently, there was a progressive diminution of the blood chloride concentration until the dehydration immediately prior to death. The preoperative level was never regained, however (fig. 5, *B*).

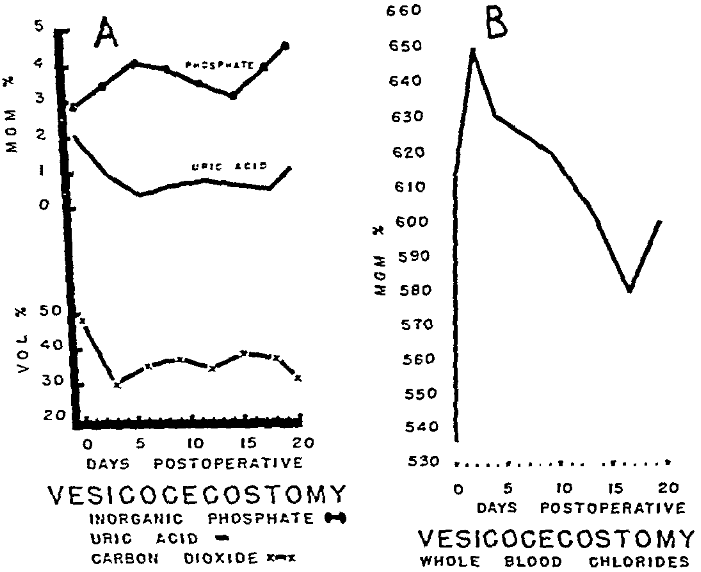


FIG. 5. *A*, vesicocecostomy. Average concentration of serum inorganic phosphorus, blood uric acid, and serum carbon dioxide combining power in 8 animals. *B*, vesicocecostomy. Average concentration of whole blood chlorides in 8 animals. Mean variation for any one day ranges from 8 to 36 mg. per 100 cc.

Excretory urograms revealed good bilateral concentration of the diodrast without evidence of dilatation or obstruction of the collecting system of the urinary tract. This was true even with an associated elevation of blood nonprotein nitrogen to 60 to 80 mg. per 100 cc and until the onset of lethargy 24 to 72 hours prior to death. Excretory urograms made at the time when blood nonprotein nitrogen was above 80 mg. per 100 cc showed no concentration of the dye on the x-ray films.

Autopsy of the animals in group 1 revealed no evidence of urinary tract obstruction or infection. The renal parenchyma, renal pelves, and ureters were normal on microscopic examination. The average weight of both kidneys was 67 gm. with a range of 59 to 77 gm. Areas of submucosal petechiae were universally present in some part of the bowel, most frequently the duodenum and lower ileum. The pericardium was not unusual on gross or microscopic examination.

Sub-group 1. Vesicocecostomy plus ileostomy. It seemed probable that the extreme deviation of blood nonprotein nitrogen exhibited by animals Nos. 6 and 7 (fig. 4, *A*) might be explained on the basis of reflux of urine through the ileocecal valve and into the ileum. Accordingly, a series of x-ray studies of diodrast enemas was carried out in 6 normal dogs. Reflux of diodrast into the terminal ileum was demonstrated in 2 of the 6 animals. This was more evident when small quantities of diodrast (50 to 90 cc) were used with low pressure gravity filling of the colon. Furthermore, the same 2 animals showed reflux of diodrast into the small bowel when the examination was repeated at a later date.

Five animals were then subjected to vesicocecostomy with simultaneous cutaneous ileostomy and ligation of the terminal ileum at the ileocecal valve (fig 6).

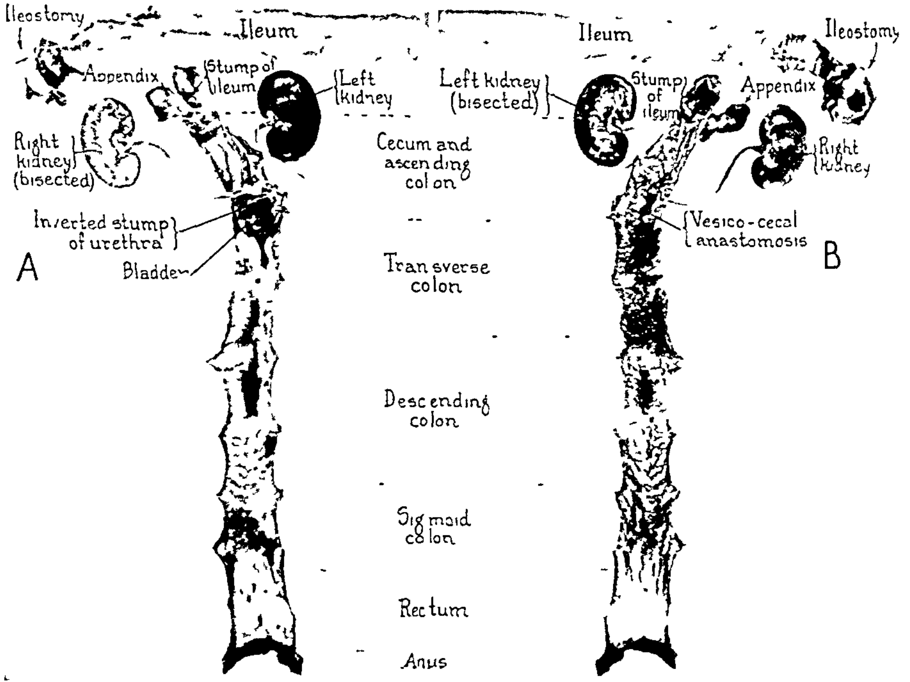


FIG 6 Vesicocecostomy with associated ileostomy Animal No 30, twenty-one days postoperative *A*, ventral view *B*, dorsal view Bowel has been opened along line of mesenteric attachment Ventral half of right kidney and dorsal half of left kidney have been removed

The general clinical course of these animals was similar to the group 1 animals which had not had an ileostomy. They appeared quite well until 24 to 72 hours prior to death, when dehydration and lethargy developed rapidly. Coma and death occurred on the sixteenth to the twenty-first postoperative day (fig. 7).

The rise in blood nonprotein nitrogen, urea nitrogen, and creatinine was closely parallel to all animals in group 1 except Nos 6 and 7. (Compare figs 4, *B* and 7.)

The blood uric acid concentration was depressed and remained at a level of 0 5 to 0.7 mg. per 100 cc until the terminal stage of dehydration.

Serum inorganic phosphorus remained within the normal range of variation until just prior to death.

Whole blood chlorides exhibited an irregular decline from the preoperative average of 576 mg. per 100 cc to levels of 490 to 540 mg. per 100 cc prior to death. There was little correlation between chloride concentration of the various individuals.

The serum carbon dioxide combining power was depressed to an average of 40 volumes per 100 cc on the third postoperative day and remained at that level with slight variation until just prior to death.

Excretory urograms revealed good bilateral concentration of the dye without evidence of obstruction to free flow of urine into the colon.

There was no evidence of urinary tract obstruction or infection at postmortem examination. Microscopic study of the renal parenchyma, renal pelves, and ureters revealed no abnormal findings. Average weight of both kidneys was 62 gm. (range 55 to 74 gm.). Minute submucosal petechiae were observed constantly in the stomach, small bowel, and occasionally in the colon.

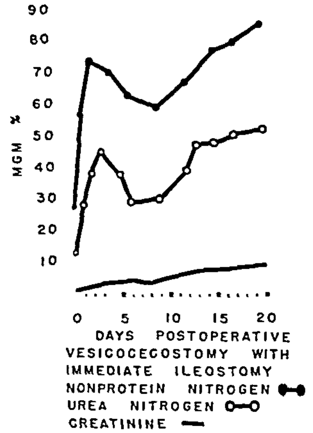


FIG. 7. Vesicocecostomy with associated ileostomy. Average concentration of blood nonprotein nitrogen, blood urea nitrogen, and creatinine in 5 animals.

Group 2. Vesicosigmoidostomy. Group 2 animals in which only vesicosigmoidostomy was done promptly returned to normal appetite and activity (fig. 8). This group was followed for a period of 60 days postoperatively. During this time there was a sustained increase in urinary output of approximately 5 times the preoperative volume. The average 24 hour urine volume preoperatively was 110 cc, with individual variations from 60 to 210 cc. Postoperatively the average 24-hour volume was 580 cc, with individual variations of 220 to 1100 cc.

All animals in this group gained weight slowly but progressively. The average gain was 4.5 pounds per animal for the 60-day period.

Excretory urograms made on the fifth to the ninth postoperative day and repeated on the thirtieth to the sixtieth day revealed prompt appearance of the dye in the 5 minute films without demonstrable anatomical abnormality of the urinary tract.

Immediately postoperative there was an increase in the blood nonprotein nitrogen to an average value of 94 mg. per 100 cc on the fifth postoperative day. This was followed by a gradual but progressive decline to approach the normal on the thirty-third day. The average value for the group remained just above the upper limits of normal throughout the 60 days of follow-up observation (fig. 9, *B*). The individual variations are shown in fig. 11. The peak elevation in blood nonprotein nitrogen varied from 68 to 104 mg. per 100 cc and occurred from the third to the tenth postoperative day.

The accompanying rise in urea nitrogen is demonstrated in figure 9, *B*. As in group 1, the average values for the urea nitrogen are misleading. The variations of the individual determinations in urea nitrogen were unpredictable and ranged from one fourth to two thirds of the total nonprotein nitrogen concentration. The standard deviation for the urea nitrogen on any one day in figure 9, *B* varies from 2 to 18 units.

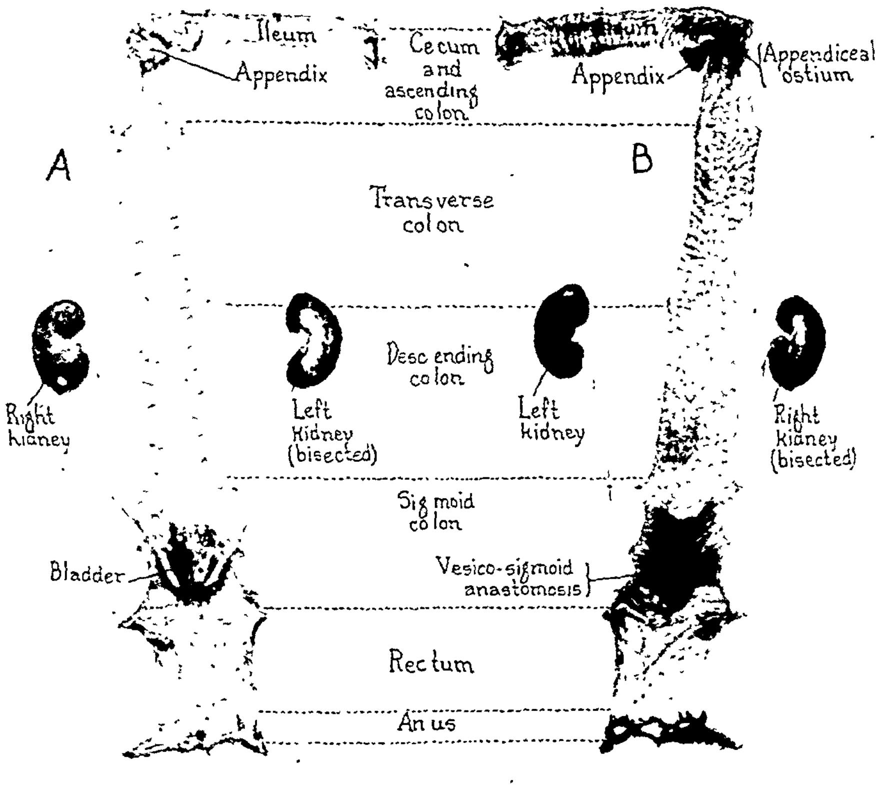
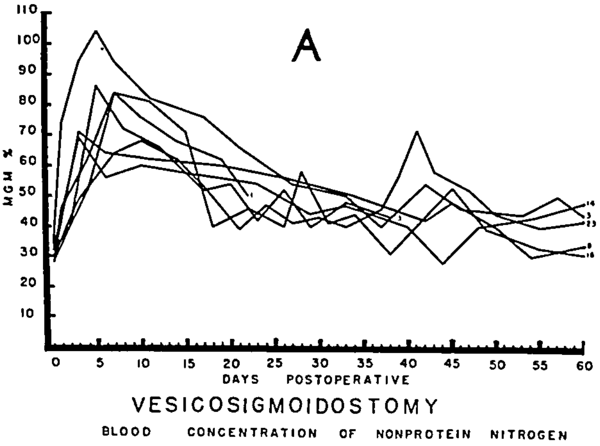


FIG. 8. Vesicosigmoidostomy. Animal No. 8, 60 days postoperative. *A*, ventral view. *B*, dorsal view. Bowel has been opened along line of mesenteric attachment. Ventral half of left kidney and dorsal half of right kidney have been removed.

The blood creatinine increased progressively to a peak of 7 mg. per 100 cc on the fifth postoperative day and returned gradually to normal by the twenty-first day. The standard deviation for creatinine in figure 9, *B* is less than 2 units.

Blood uric acid determinations showed a prompt depression to less than one-half the preoperative concentration. The average concentration remained below the preoperative level throughout the 60 days of observation (fig. 10, *A*). After the thirty-third postoperative day individual determinations occasionally approached the normal but these levels were never sustained.

There was no significant change in the serum inorganic phosphorus during the postoperative period (fig. 10, *A*).



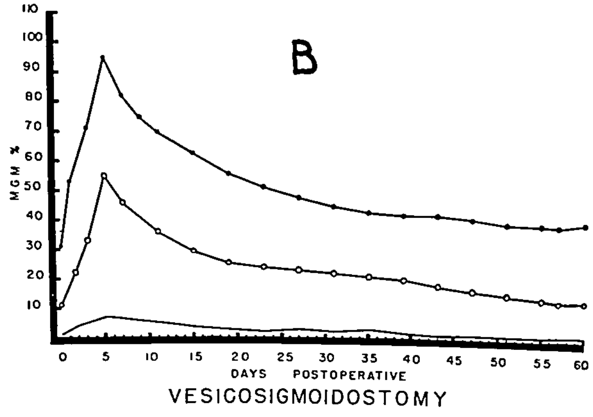


FIG. 9. *A*, vesicosigmoidostomy. Individual variations in blood nonprotein nitrogen. Small figures indicate number of experiment. For clarity, not all individuals nor all determinations of any one individual are included. Range of extreme variation is presented. *B*, vesicosigmoidostomy. Average concentrations of blood nonprotein nitrogen, urea nitrogen and creatinine in 10 animals.

The serum carbon dioxide combining power decreased to an average low of 32 volumes per 100 cc on the seventh postoperative day and remained approximately 40 volumes per 100 cc throughout the postoperative period of observation. This value was remarkably constant and in no instance did the individual regain the preoperative level (fig. 10, *B*).

There was a prompt elevation in whole blood chlorides to an average of 639 mg. per 100 cc with a progressive return to approach the normal. Although the average level of blood chlorides remained above the preoperative average of 560 mg. per on the thirty-third day. The average value for the group remained just above the upper limits of normal throughout the 60 days of follow-up observation (fig. 9, *B*). The individual variations are shown in fig. 11. The peak elevation in blood nonprotein nitrogen varied from 68 to 104 mg. per 100 cc and occurred from the third to the tenth postoperative day.

The accompanying rise in urea nitrogen is demonstrated in figure 9, *B*. As in group 1, the average values for the urea nitrogen are misleading. The variations of the individual determinations in urea nitrogen were unpredictable and ranged from one fourth to two thirds of the total nonprotein nitrogen concentration. The standard deviation for the urea nitrogen on any one day in figure 9, *B* varies from 2 to 18 units.

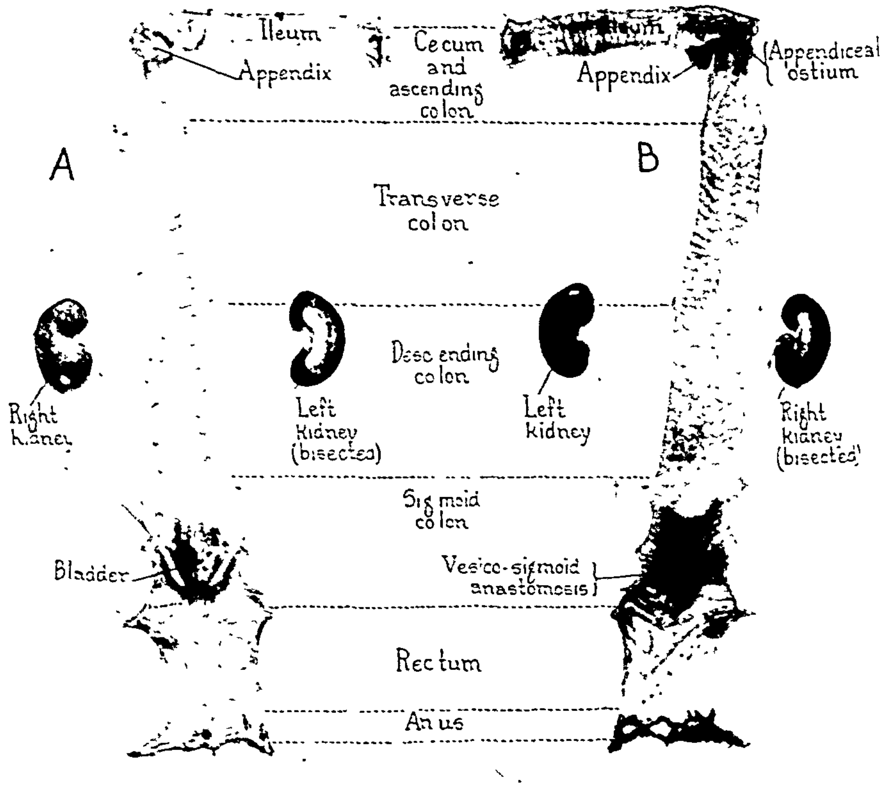
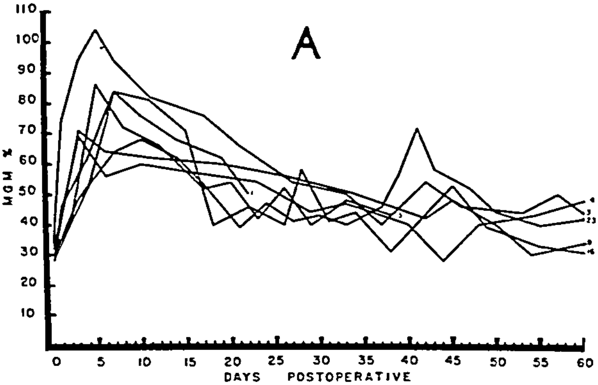


FIG. 8 Vesicosigmoidostomy. Animal No. 8, 60 days postoperative *A*, ventral view. *B*, dorsal view. Bowel has been opened along line of mesenteric attachment. Ventral half of left kidney and dorsal half of right kidney have been removed.

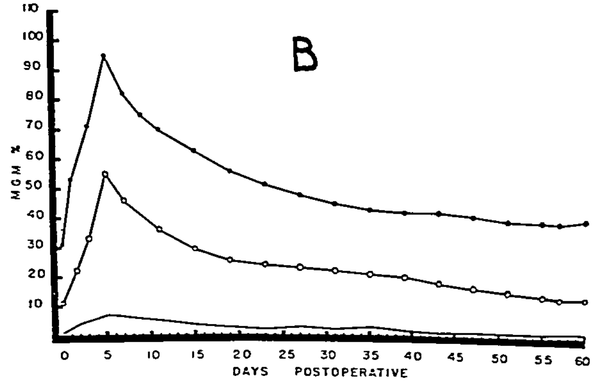
The blood creatinine increased progressively to a peak of 7 mg. per 100 cc on the fifth postoperative day and returned gradually to normal by the twenty-first day. The standard deviation for creatinine in figure 9, *B* is less than 2 units.

Blood uric acid determinations showed a prompt depression to less than one-half the preoperative concentration. The average concentration remained below the preoperative level throughout the 60 days of observation (fig. 10, *A*). After the thirty-third postoperative day individual determinations occasionally approached the normal but these levels were never sustained.

There was no significant change in the serum inorganic phosphorus during the postoperative period (fig. 10, *A*).



VESICOSIGMOIDOSTOMY
BLOOD CONCENTRATION OF NONPROTEIN NITROGEN



VESICOSIGMOIDOSTOMY
NONPROTEIN NITROGEN •—• UREA NITROGEN o—o CREATININE —

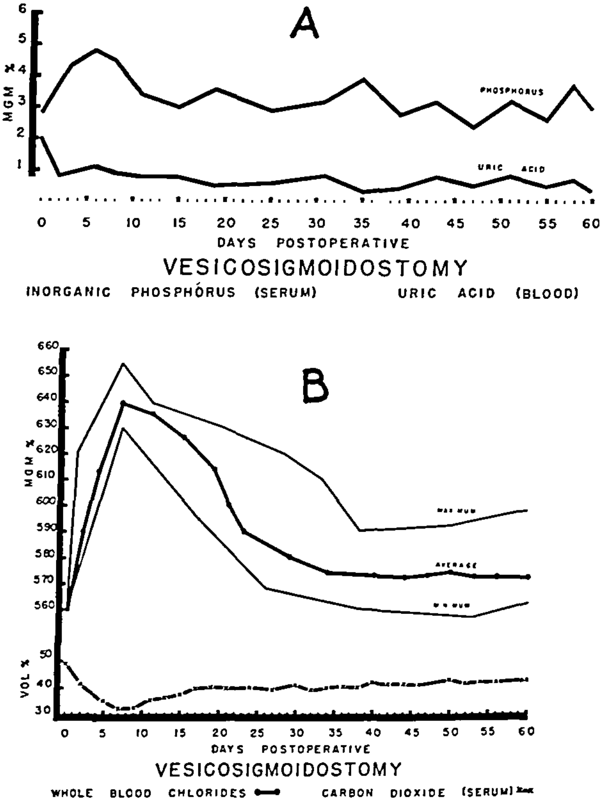
FIG. 9. *A*, vesicosigmoidostomy. Individual variations in blood nonprotein nitrogen. Small figures indicate number of experiment. For clarity, not all individuals nor all determinations of any one individual are included. Range of extreme variation is presented. *B*, vesicosigmoidostomy. Average concentrations of blood nonprotein nitrogen, urea nitrogen and creatinine in 10 animals.

The serum carbon dioxide combining power decreased to an average low of 32 volumes per 100 cc on the seventh postoperative day and remained approximately 40 volumes per 100 cc throughout the postoperative period of observation. This value was remarkably constant and in no instance did the individual regain the preoperative level (fig. 10, *B*).

There was a prompt elevation in whole blood chlorides to an average of 639 mg. per 100 cc with a progressive return to approach the normal. Although the average level of blood chlorides remained above the preoperative average of 560 mg. per

100 cc, the range of extremes was within the extreme variation encountered in the preoperative period, that is, 510 to 620 mg. per 100 cc (fig. 10, *B*).

Two animals in the group of 10 vesicosigmoidostomies died during the 60-day period of observation. Both animals suddenly became lethargic, refused food and water, and developed physical signs of severe dehydration. There was a progressive elevation in blood nonprotein nitrogen and urea nitrogen. Coma and death occurred 36 to 72 hours after the onset of clinical symptoms. Death occurred in dog No. 1 on the twenty-fifth day and in dog No. 13 on the forty-first day. After the close of the 60-day period of observation dog No. 43 died on the ninety-third postoperative day. The blood nonprotein nitrogen levels of dogs Nos. 1 and 43 are shown in figure 11.



VESICOSIGMOIDOSTOMY
INORGANIC PHOSPHORUS (SERUM) URIC ACID (BLOOD)

VESICOSIGMOIDOSTOMY
WHOLE BLOOD CHLORIDES CARBON DIOXIDE (SERUM)

FIG. 10. *A*, vesicosigmoidostomy. Average concentrations of serum inorganic phosphorus and blood uric acid in 10 animals. *B*, vesicosigmoidostomy. Average concentrations of whole blood chlorides in mg. per 100 cc. and of serum carbon dioxide combining power in volumes per 100 cc as shown in 10 animals. Maximum and minimum lines on chloride graph refer to variations in mean results and not to individual determinations.

Autopsies of these 3 animals which expired and of 5 which were sacrificed at intervals of 2 to 6 months revealed no evidence of any anatomical abnormality in the kidneys or ureters. Microscopic sections of the renal parenchyma, renal pelves, and ureters revealed no evidence of infection or other histopathologic change. The average weight of the two kidneys in this series was 98.4 gm. with a range from 90 to 112 gm.

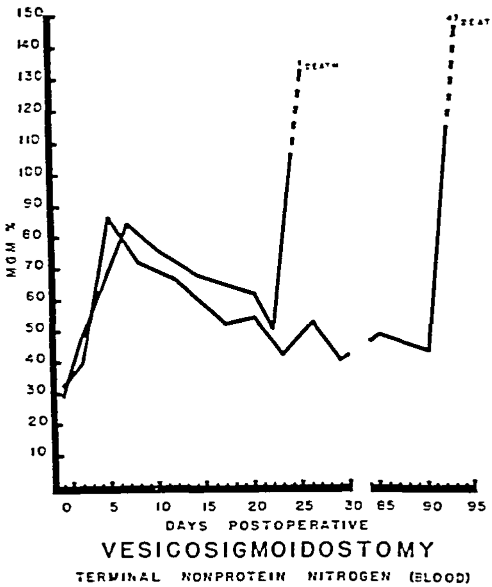


FIG. 11. Vesicosigmoidostomy. Blood nonprotein nitrogen concentrations of 2 animals that died during experiment. Small figures indicate number of animal. Interrupted lines are projections of trend in concentration between last determination and time of death.

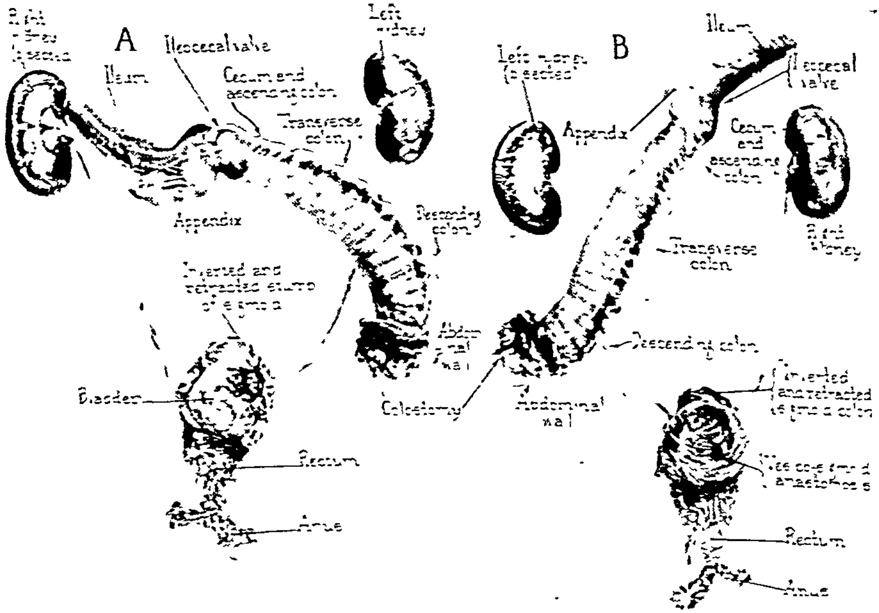


FIG. 12. Vesicosigmoidostomy with cutaneous sigmoidostomy. Dog No. 18, thirty days postoperative. *A*, ventral view. *B*, dorsal view. Isolated segment of sigmoid and rectum has been opened along mesentery; the remaining bowel is intact. Comparatively short length of bowel is due to contraction in fresh specimen.

100 cc, the range of extremes was within the extreme variation encountered in the preoperative period, that is, 510 to 620 mg. per 100 cc (fig. 10, *B*).

Two animals in the group of 10 vesicosigmoidostomies died during the 60-day period of observation. Both animals suddenly became lethargic, refused food and water, and developed physical signs of severe dehydration. There was a progressive elevation in blood nonprotein nitrogen and urea nitrogen. Coma and death occurred 36 to 72 hours after the onset of clinical symptoms. Death occurred in dog No. 1 on the twenty-fifth day and in dog No. 13 on the forty-first day. After the close of the 60-day period of observation dog No. 43 died on the ninety-third postoperative day. The blood nonprotein nitrogen levels of dogs Nos. 1 and 43 are shown in figure 11.

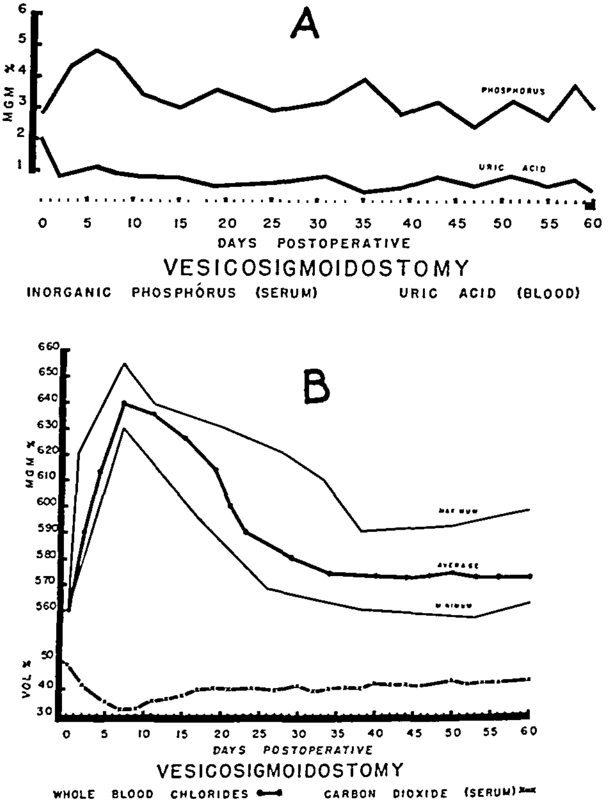


FIG. 10. *A*, vesicosigmoidostomy. Average concentrations of serum inorganic phosphorus and blood uric acid in 10 animals. *B*, vesicosigmoidostomy. Average concentrations of whole blood chlorides in mg. per 100 cc. and of serum carbon dioxide combining power in volumes per 100 cc as shown in 10 animals. Maximum and minimum lines on *chloride* graph refer to variations in mean results and not to individual determinations.

Autopsies of these 3 animals which expired and of 5 which were sacrificed at intervals of 2 to 6 months revealed no evidence of any anatomical abnormality in the kidneys or ureters. Microscopic sections of the renal parenchyma, renal pelves, and ureters revealed no evidence of infection or other histopathologic change. The average weight of the two kidneys in this series was 98.4 gm. with a range from 90 to 112 gm.

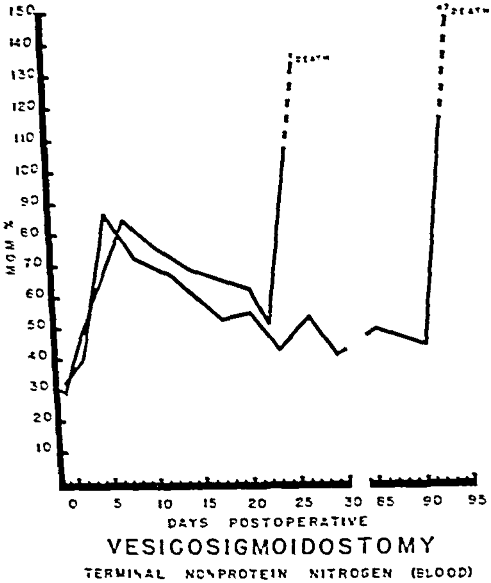


FIG. 11. Vesicosigmoidostomy. Blood nonprotein nitrogen concentrations of 2 animals that died during experiment. Small figures indicate number of animal. Interrupted lines are projections of trend in concentration between last determination and time of death.

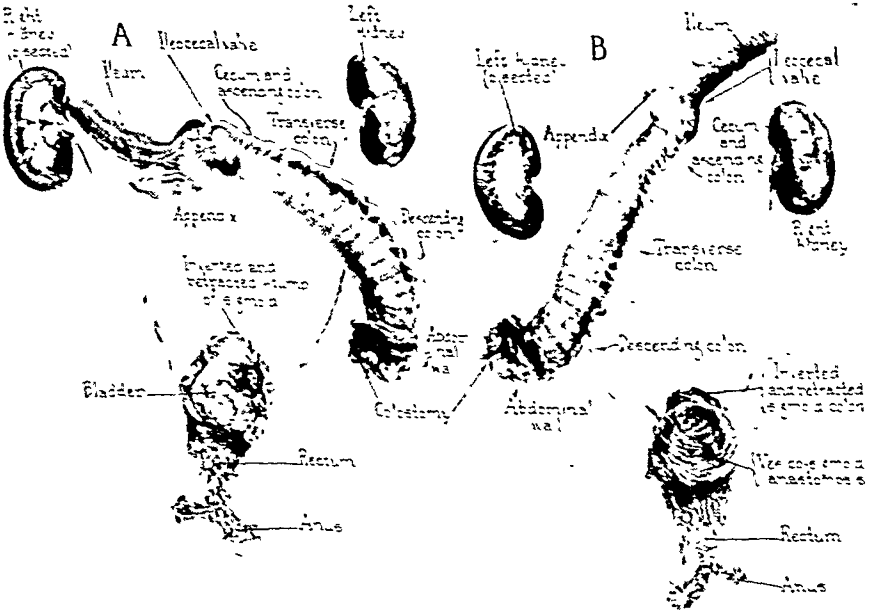


FIG. 12. Vesicosigmoidostomy with cutaneous sigmoidostomy. Dog No. 18, thirty days postoperative. *A*, ventral view. *B*, dorsal view. Isolated segment of sigmoid and rectum has been opened along mesentery; the remaining bowel is intact. Comparatively short length of bowel is due to contraction in fresh specimen.

The remaining 2 animals in this series are alive at 9 months without evidence of urinary tract infection or obstruction on intravenous urography.

Sub-group 2. Vesicosigmoidostomy plus cutaneous sigmoidostomy. Five animals in group 2 were subjected to vesicosigmoidostomy and simultaneous cutaneous colostomy. The sigmoid colon was divided cephalad to the site of vesicosigmoid anastomosis and the fecal stream diverted by cutaneous descending colostomy. Reflux of urine was prevented by ligation and inversion of the stump of the sigmoid (fig. 12).

The average postoperative increase in blood nonprotein nitrogen in this group was 41 mg. per 100 cc on the first postoperative day with a prompt return to normal by the fourth day (fig. 13). The nonprotein nitrogen compared favorably with the control series (fig. 2).

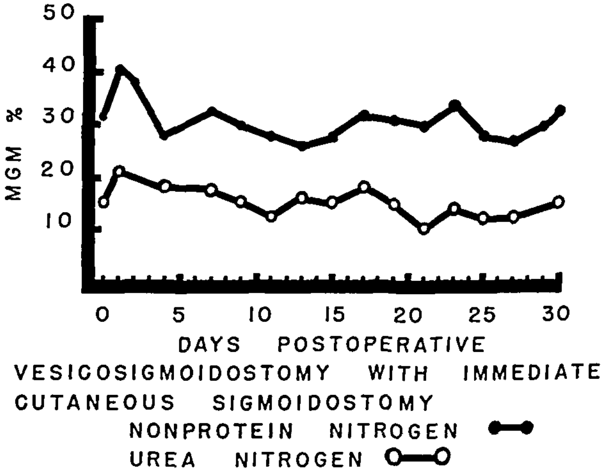


FIG. 13. Vesicosigmoidostomy with immediate cutaneous sigmoidostomy. Average concentration of blood nonprotein nitrogen and urea nitrogen in 5 animals.

The individual blood urea nitrogen determinations comprised 40 to 56 per cent of the total blood nonprotein nitrogen throughout the series.

Blood uric acid was not depressed but remained at an average value of 2.1 mg. per 100 cc with a range of 1.0 to 2.7 mg. per 100 cc.

The serum inorganic phosphorus concentration remained between 1.8 and 4.0 mg. per 100 cc.

Serum carbon dioxide combining power remained within normal limits. The average value was 47 volumes per 100 cc with a range of 41 to 53 volumes per 100 cc.

Whole blood chloride concentration increased to the upper limits of normal (628 mg. per 100 cc) but promptly returned to within normal degrees of variation and remained so throughout the experiment.

Excretory urograms revealed prompt appearance of the diodrast in the 5 minute films with no demonstrable abnormality of the urinary tract. The collection of the dye in the isolated sigmoid and rectum was well visualized in every instance.

The animals were sacrificed on the thirtieth postoperative day. No demonstrable abnormality was noted on gross examination of the urinary or gastro-intestinal tracts, above or below the anastomosis. Microscopic examination of the renal parenchyma, renal pelves and ureters revealed no evidence of infection or other histopathologic changes. The average weight of both kidneys was 58 gm., with a range of 50 to 66 gm.

Three animals were subjected to vesicosigmoidostomy with a cutaneous sigmoidostomy and isolation of the bowel containing the anastomosis as a secondary procedure 5 to 12 days later (fig. 12).

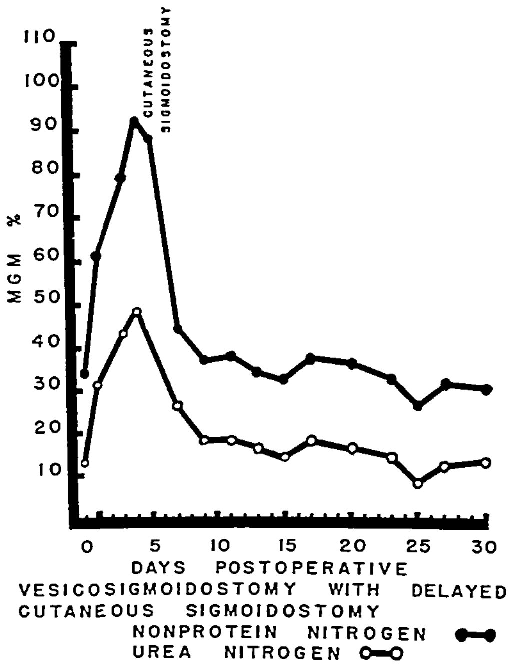


FIG. 14. Vesicosigmoidostomy with delayed cutaneous sigmoidostomy on fifth day. Dog No. 18.

The prompt return of the blood nonprotein nitrogen and urea nitrogen to normal limits following isolation of the sigmoid and rectum is demonstrated in figure 14.

Creatinine was reduced to less than 2 mg. per 100 cc of whole blood in less than 6 days after the second operation and remained within normal limits throughout the 30 days of observation.

Blood uric acid was depressed to an average concentration of 0.7 mg. per 100 cc at the time of cutaneous sigmoidostomy. Five days after the secondary procedure the blood uric acid had increased to 2.4 or more mg. per 100 cc and remained above 1.5 mg. per 100 cc for the remainder of the experiment.

Serum inorganic phosphorus remained between 1.8 and 3.6 mg. per 100 cc throughout the experiment.

The carbon dioxide combining power of the serum was an average of 33 volumes per 100 cc at the time of the second operation. This value increased immediately to an average of 45 volumes per 100 cc and remained within the normal range of 40 to 50 volumes per 100 cc.

Whole blood chlorides remained within a range of 525 to 580 mg. per 100 cc.

Excretory urograms revealed good concentration of the diodrast both in the renal pelves and in the isolated sigmoid and rectum.

The animals were sacrificed 30 days after the initial operation. There was no gross evidence of infection or obstruction to drainage within the urinary tract. Microscopic study of the renal pelves, renal parenchyma, and ureters revealed no abnormalities. No petechiae or other unusual changes were demonstrated in the gastro-intestinal tract either above or below the colostomy.

DISCUSSION

The concentration of the chief nonprotein nitrogenous constituents (urea, ammonia, amino-acids, uric acid, creatinine, and creatine) in the blood of the normal animal is chiefly determined by the balance between the rate of protein catabolism and the urinary output of nitrogen. In the postoperative animal a third factor was introduced: the absorption of nitrogenous compounds from the colon. An effort was made to keep the first two factors as near the usual ratio as possible by furnishing a palatable diet, daily exercise, and adequate oral and parenteral fluid intake. The success of this effort to maintain normal protein intake was reflected in the progressive gain in body weight in all animals during the postoperative period. The large urine volume, in view of the normal renal function and anatomy demonstrated both preoperatively and postmortem, was indicative of a normal urinary output of nitrogen. The variable factor in the postoperative animal was therefore the degree of absorption of nitrogenous compounds from the large bowel. The validity of this assumption is borne out by comparison of the results in the two groups of animals.

The postoperative increase in blood nonprotein nitrogen, urea nitrogen, and creatinine could not have been due to renal failure. The close parallelism of the course of each individual animal, as shown in figures 4, *A* and 9, *A*, would necessitate an equal degree of renal failure, a most unlikely presumption. The volume of urine and prompt excretion of diodrast in good concentration were not compatible with marked impairment of renal function. Furthermore, no demonstrable histopathologic changes were present in the renal parenchyma of any animal in the series. Experimental renal failure, either by arterial occlusion or ureteral obstruction, is characterized by an increase in plasma inorganic phosphorus and blood uric acid. Indeed, an increase in blood uric acid is usually the earliest biochemical evidence of renal failure. Neither value was increased in this series of experiments.

The use of sodium pentabarbitol anesthesia has been shown to cause no evidence of protein destruction or diminished renal function, even after much larger dosage than was used in these experiments. This was substantiated by the 5 control animals in this series (fig. 2).

In group 1 animals (vesicocecostomy) the increase in blood nonprotein nitrogen shown by animals Nos. 6 and 7 in figure 4, *A* was probably due to additional absorption from reflux of urine into the ileum, since the curve shown by these animals was more elevated than that of the comparable group with associated ileostomy (fig. 7). Furthermore, the elevation in nonprotein nitrogen that occurred in the other animals with simple vesicocecostomy (fig. 4, *A*) was due largely or entirely to absorption from the colon only, since the curve for these animals closely resembles that for the group with ileostomy. (Compare figs. 4, *B* and 7.)

In group 2 (vesicosigmoidostomy) the abrupt increase in nonprotein nitrogen suggested absorption of nitrogenous compounds. The progressive return of the blood level of nitrogenous compounds to a concentration approaching the normal indicated some type of compensation. It is conceivable that compensation was accomplished by increase in the concentration of nitrogenous products in the urine. The quantity of such products lost from the body would be directly proportional to the concentration in the urine when urine volume and frequency of emptying the colon remained constant. Increased absorption from the bowel would probably occur as the concentration of nitrogenous products increased in the contained urine. Such reabsorption, however, could never keep pace with increased renal excretion if the surface area of the involved bowel mucosa remained fairly constant. The quantity of nitrogenous products presented to the kidneys for excretion each 24 hours was a relatively constant amount and increased concentration in the urine that entered the bowel must eventually result in removal of a large proportion of these substances from the body. Involvement of a large area of bowel, such as the entire colon, or a more permeable area, such as the cecum, could conceivably promote reabsorption of nitrogenous and toxic compounds at a rate greater than could be compensated for by maximum renal excretion. Such would appear to be the case when figures 4, *B* and 9, *B* are compared. The essential difference between groups 1 and 2 was the ability of group 2 to compensate for the added burden presented to the kidneys. The balance of compensation by group 2 could be upset, however, as shown in figure 11. The course of these animals was then strikingly similar to the terminal course of group 1, a condition that may be described as a state of renal decompensation.

The marked difference in weight of the total renal tissue in the two groups may indicate compensatory hypertrophy in group 2, in which the kidneys averaged 45 per cent greater in weight than group 1 (67 gm. in group 1 as compared to 98 gm. in group 2). Microscopic examination did not furnish unequivocal evidence of hypertrophy in either group.

Under no circumstances can a literal interpretation be applied to the changes in blood creatinine reported in these experiments. The increase in creatinine can be regarded only as an increase in those chromogenic materials which give the Jaffe reaction. As shown by the specific enzyme method of Miller and Dubos the concentration of true creatinine in plasma is only about half as great as the Jaffe reaction indicates, and in the erythrocytes the chromogenic material is only 30 to 50 per cent true creatinine. The diffusion of creatinine between the cells and serum makes interpretation even more difficult. There is also good evidence that at higher than normal blood levels of creatinine some of the true creatinine is transformed to one or more unidentified substances. The concentration of chromogenic material within the blood following diversion of urine to the cecum and to the sigmoid colon demonstrated an appreciable difference between the two groups. The significance of this variation cannot be interpreted with the analytical methods now available.

The depression of plasma levels of uric acid in both groups may have been a reflection of the ability of the liver to convert uric acid to allantoin. Uric acid accounts for only 0.75 per cent of the total nitrogen in the urine of dogs on a diet similar to that of animals in this series. The low plasma levels may have been due to the ability of the kidney to increase the excretion of uric acid, particularly in the presence of increased plasma concentration of other nitrogenous compounds.

The ability of both groups of animals to maintain normal serum inorganic phosphorus levels may be due to little or no absorption or to the ability of the dog kidney to excrete phosphate independently of the rate of glomerular filtration.

The persistent depression of the normal levels of serum carbon dioxide combining power was comparable in the two groups. This may have been due to the loss of base both from the diarrhea induced by flushing of the colon with urine and by inefficient loss of base from a kidney functioning at maximum excretory capacity. The retention of acid radicals may have been a contributing factor. In any event, the animal was partially able to compensate for the change, since the initial depression of carbon dioxide combining power returned to a constant subnormal level and was maintained until the terminal stages of severe dehydration (figs. 5, *A* and 10, *B*).

The postoperative increase in whole blood chlorides in both groups may have been a result of intravenous chloride administration, although the quantity of sodium chloride so given was calculated as nearly as possible to match the loss by vomiting and decreased intake. In no instance was intravenous therapy extended more than 72 hours after operation. Figures 5, *B* and 10, *B* are drawn to the same scale as all other figures in this series. However, they are deceptive unless it is kept in mind that a variation in serum chlorides of 100 mg. per 100 cc is not so significant as a variation of 10 mg. per 100 cc of blood nonprotein nitrogen. The increase in chlorides in both groups was little more than the upper limits of normal variation. In group 1 there was progressive readjustment of chlorides to approach the normal, even while nonprotein nitrogen, urea nitrogen, and creatinine blood concentrations were progressively increased.

Cause of death in the group 1 animals is not clear. It has no etiological relation to any of the chemical constituents of the blood studied in this report. Death occurred with the signs of severe dehydration. The accumulation of urea* and other osmotically active substances within the body fluids would certainly augment the effects of dehydration from decreased intake or excessive loss of fluid. It is conceivable that accumulation of osmotically active substances would result in a greater output of urine and thus establish a cycle which eventually resulted in the terminal picture of dehydration markedly augmented.

The absorption of toxic substances excreted in the urine or formed in the colon must also be considered. Normally 30 to 90 per cent of phenol and phenol derivative are excreted in the urine, and retention of phenols has been described as a major cause of depression in renal failure. The bacterial decomposition of urea and absorption of ammonia may have produced toxic symptoms and have accounted for the wide fluctuations of blood urea levels in both group 1 and group 2. Oral ingestion of ammonium chloride 1 to 2 gm. per pound of body weight will exactly duplicate in normal dogs the increase in blood nonprotein nitrogen and chloride, with depression of plasma carbon dioxide combining power demonstrated in group 2.

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* Although urea diffuses freely into lymph, transudates, and cells of the body, it contributes to the osmotic pressure of all alike.

Whatever the immediate cause, death was similar to that of acute uremia in the rapid progression of muscular incoordination, coma, and death with elevated blood nonprotein nitrogen. The absence of vomiting and muscle twitching with normal blood levels of uric acid, inorganic phosphorus, and calcium were unlike terminal true uremia.

One of the most important observations in this group of experiments was the complete absence of any evidence of urinary tract infection or hydronephrosis. A total of 25 animals were followed 1 to 2 months after vesicocolic anastomosis with no evidence clinically or at postmortem examination of urinary tract infection or hydronephrosis. Eight animals were followed 2 to 9 months after vesicosigmoidostomy without evidence of infection or dilatation of the urinary tract. Such a series strongly suggests that the normal anatomical relations of the ureterovesical junction exert an effective valvular or even sphincteric action. Whatever the mechanism it is quite effective in promoting the flow of urine from the renal pelvis into the bladder or colon without reflux of urine into the ureter and the sequelae of stasis of urine, hydronephrosis, and urinary tract obstruction. Duplication of this valve-like action as advocated by Coffey is an important aspect of the successful ureterosigmoidostomy. A modified form of the Maydl operation may have a limited but useful application in diversion of the urinary stream into the sigmoid colon for other than malignant pathological states.

SUMMARY

Following vesicocolic anastomosis there is good evidence that some chloride and nitrogenous constituents of urine are absorbed from the colon of the experimental animal (dog). Blood uric acid concentration is reduced below normal. Serum carbon dioxide combining power is depressed and remains at the lower limits of normal. Serum inorganic phosphorus remains within normal limits.

The degree of absorption is directly proportional to the surface area of the involved bowel and the duration of contact with the contained urine.

Absorption is probably most rapid from the cecum and adjacent colon, diminishing progressively to little or no absorption from the rectum.

Diversion of the entire urinary stream into the cecum results in death of the animal with elevated blood nonprotein nitrogen and signs of acute uremic intoxication.

Following diversion of the entire urinary stream into the sigmoid colon the normal reserve of renal function permits compensation for absorption of nitrogenous compounds from reflux of urine into the adjacent bowel. This compensation is imperfect but not incompatible with life for long periods.

The oblique course of the ureters through the bladder wall in the normal anatomical arrangement provides an effective valvular barrier to urinary stasis with its sequelae of hydronephrosis and pyelonephritis.

CONCLUSIONS

The longevity of the experimental animal (dog) is greatly reduced following diversion of the entire urinary stream into the cecum as compared with the long life expectancy following diversion of the urinary stream into the sigmoid colon.

The site of election for transplantation of the ureters to the bowel is as low in the sigmoid colon as possible. Ureterocecostomy is never justifiable.

The anatomical relations of the normal ureterovesical junction should be preserved or duplicated as accurately as possible in establishing a ureterosigmoidostomy.

Following ureterosigmoid anastomosis careful attention to constant rectal drainage is important during early convalescence. Such drainage during sleep may be necessary or desirable far beyond the usual period of hospitalization.

REFERENCES

Ayer, J. L., Schiess, W. A. and Pitts, R. F.: Independence of phosphate reabsorption and glomerular filtration in the dog. Am. J. Physiol. **151**: 168–173, 1947.

Baird, J. S., Scott, R. L. and Spencer, R. D.: Studies on the transplantation of the ureters into the intestines. Surg., Gynec. & Obst., **24**: 482–484, 1917.

Baker, Z. and Miller, B. F.: The distribution of creatine and creatinine in the tissues of the rat, dog and monkey. J. Biol. Chem., **130**: 393, 1939.

Bergman, H. C. and Drury, D. R.: A study of acute renal insufficiency. J. Clin. Investigation, **18**: 777, 1939.

Bollman, J. L. and Mann, F. C.: The nitrogenous constituents of the blood following experimental transplantation of the ureters into different levels of the intestine. Proc. Staff Meet., Mayo Clin., **2**: 134, 1927.

Bollman, J. L. and Mann, F. C.: Nitrogenous constituents of blood following transplantation of ureters into different levels of the intestine. Proc. Soc. Exper. Biol. & Med., **24**: 923, 1927.

Bollman, J. L. and Mann, F. C.: Compensatory hypertrophy of the remaining kidney after nephrectomy following transplantation its ureter into the duodenum. Arch. Path., **19**: 28, 1935.

Brunschwig, A.: Complete excision of pelvic viscera in the male for advanced carcinoma of the sigmoid invading the urinary bladder. Ann. Surg., **129**: 499, 1949.

Byers, S. O., Friedman, M. and Garfield, M. M.: Role of the liver and kidney in blood uric acid and allantoin metabolism. Am. J. Physiol., **150**: 677, 1947.

Coffey, R. C.: Transplantation of the ureters into the large intestine. Surg., Gynec. & Obst., **47**: 593, 1928.

Cooke, J. V., Rodenbaugh, F. H. and Whipple, G. H.: Intestinal obstruction: A study of the non-coagulable nitrogen of the blood. J. Exper. Med., **23**: 717, 1916.

Daft, F. S., Robscheit-Robbins, F. S. and Whipple, G. H.: Abscess nitrogen metabolism in anemic and non-anemic dog. J. Biol. Chem., **121**: 45, 1937.

Douglas, H. L. and Edwards, L. W.: Experimental studies of uretero-intestinal anastomosis. Ann. Surg., **104**: 87, 1936.

Fiske, C. H. and SubbaRow, Y.: The colorimetric determination of phosphorus. J. Biol. Chem., **66**: 375, 1925.

Folin, O. J.: Simplified process for the preparation of a correct uric acid reagent. J. Biol. Chem., **106**: 311, 1934.

Forster, R. P.: An examination of some factors which alter glomerular activity in the rabbit kidney. Am. J. Physiol., **15** : 523, 1947.

Fortner, J. G. and Kieffer, J. H.: Ureteroduodenal anastomosis in dogs. J. Urol., **59**: 31, 1948.

Geer, W. A. and Dragstedt, L. R.: Effect of deviating urine into the blood stream and intestines of dog. Ann. Surg., 108: 263, 1938.

Gentzkow, C. J.: An accurate method for determination of blood urea nitrogen by direct nesslerization. J. Biol. Chem., 143: 540, 1942.

Glaubitz, G.: Uber eiweisszerfall bei Vergiftungen. Z. ges. exp. Med., 25: 230, 1921.

Hawk, P. B., Osser, B. L. and Summerson, W. H.: Practical Physiological Chemistry. Philadelphia: Blakiston Co., 1947, 12th ed., p. 509.

Hartman, F. W.: Methods and effects of increasing the urinary constituents in the body. J. Exper. Med., 58: 649, 1933.

Hess, E.: Transplantation of the ureters to the bowel. J. Internat. Coll Surg., 9: 517, 1946.

Hinman, F. A., and Belt, E.: An experimental study of ureteroduodenostomy. J. A. M. A., 79: 1917, 1922.

Kingo, G.: A study of the nitrogen metabolism and of acidosis after the transplantation of a ureter into the duodenum of dogs. J. Exper. Med., 27: 449, 1918.

Koch, F. C. and McMeekin, T. L.: A new direct nesslerization micro-Kjeldahl method. J. Am. Chem. Soc., 46: 2066, 1924.

Mason, M. F., et al.: Mechanism of experimental uremia. Arch. Int. Med., 60: 312, 1937.

Masson, G., Corcoran, A. C. and Page, I. H: Dietary and hormonal influences in experimental uremia. J. Lab. & Clin. Med., 34: 925, 1949.

Matsumoto, M.: An experimental study on the implantation of the both ureters to the small intestine. Arch. f. Japanische Chir., 15: 299, 1938.

Matsumoto, M.: An experimental study on the implantation of the both ureters to the small intestine. Arch. f. Japanische Chir., 15: 545, 1938.

Miller, B. F. and Dubos, R.: Determination by a specific enzyme method of the creatinine content of blood and urine from normal and nephritic individuals. J. Biol. Chem., 121: 457, 1937.

Pendleton, W. R. and West, F. E.: The passage of urea between the blood and lumen of the small intestine. Am. J. Physiol., 101: 391, 1932.

Powell, K.: A method of defunctioning the bladder and rectum in advanced pelvic carcinoma. Brit. J. Surg., 36: 421, 1949.

Reid, M. R.: Uretero-venous anastomosis with observations on experimental hydronephrosis and the blood nitrogen. Bull. Johns Hopkins Hosp., 29: 55, 1918.

Robard, S.: Some factors affecting duration of life in total anuria. Proc. Soc. Exper. Biol. & Med., 59: 207, 1945.

Sauer, H. R., Blick, M. S. and Buchwald, K. W.: Changes in renal function following ureteral transplantation. Surg., Gynec. & Obst., 89: 299, 1949.

Schales, O. and Schales, S. S.: A simple and accurate method for determination of chloride in biological fluids. J. Biol. Chem., 140: 879, 1941.

Shannon, J. A. and Ranges, H. A.: On the renal tubular excretion of creatinine in normal man. J. Clin. Investigation, 20: 169, 1941.

Turner, G. G.: Transplantation of the ureters into the large bowel. Brit. M. J., 2: 535, 1943.

Van Slyke, D. D. and Cullen, G. E.: The bicarbonate concentration of the blood plasma; its significance, and its determination as a measure of acidosis. J. Biol. Chem., 30: 289, 1917.

Wells, C. W.: Blood chemistry studies in influenzal pneumonia. Arch. Int. Med., 26: 443, 1920.

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DISCUSSION

DR. CHARLES C. HIGGINS (Cleveland, Ohio): I wish to congratulate Dr. Boyce on his excellent experimental work.

The subject is particularly appropriate at the present time since, with the advent of cystectomy for the relief of certain patients with carcinoma of the bladder, the diversion of the urinary stream into the rectosigmoid is employed more frequently than it has been in past years.

Secondly, as Dr. Boyce mentioned, case reports are appearing in the literature advocating or suggesting the possibility of transplanting the right ureter into the cecum and the left ureter into the rectosigmoid. Considerable investigative work has been done, as you know, chiefly by the physiologists.

In the nineteen-thirties, Geer and Dragstedt, Bollman and Mann, Pendleton and West, and others made valuable contributions on this subject. Bollman and Mann demonstrated in the experimental laboratory that when a single ureter was transplanted into the different portions of the intestine, no changes were noted in the nitrogenous constituents of the blood. This was to be expected as the opposite normal kidney could maintain the normal urinary excretion. It did demonstrate, however, that drainage of part of the urine into the intestine was unaccompanied by changes in nitrogenous constituents of the blood, or demonstrable effects of the experimental animal.

They further stated the results with bilateral transplantation of the ureters were essentially the same as those produced by the single transplantation with the surgical removal of the opposite kidney.

Transplantation of the ureters into the colon was followed usually by an elevation of the blood urea for several days, later decreasing to within normal levels.

Ureteral transplantation in the rectosigmoid was followed by rise in the blood urea nitrogen with no significant alterations in the other blood constituents studied. Again there is a return in the blood urea to approximately normal levels.

When the ureters are transplanted into the jejunum, ileum or duodenum, observers have reported identical findings. There is a rapid rise in the blood urea and the animals live for 14 to 21 days.

The striking observation is the lack of clinical symptoms in spite of the pronounced elevation of the blood urea until the last two or three days of life.

Baird, Scott and Spencer showed when both ureters were transplanted into the duodenum of dogs, the urine is almost completely reabsorbed, the nonprotein nitrogen of the blood rises to high levels, and the dogs die of uremia in a few days.

In 1938, Geer and Dragstedt anastomosed the bladder to the ileum, the technique similar to that discussed by Dr. Boyce today. The former observers stated a definite and sustained elevation in the nonprotein nitrogen occurred in each case following operation.

Also, in 1938, Geer and Dragstedt observed experimentally that as the urine from one kidney was diverted directly into the vena cava by uniting the ureter and lumbar vein, no toxic symptoms developed, the blood nonprotein nitrogen remained within normal limits, and there was no rise in the arterial blood pressure.

Pendleton and West demonstrated that urea passed from the blood into the fluid within the lumen of the bowel and vice versa, readily and in appreciable amounts.

Hartman, in 1933, produced a urinary fistula into the intestinal tract and found that degenerative changes were produced in the kidneys by an increase in the urinary constituents in the body; hypertrophy of the kidneys accompanied or preceded the degenerative changes.

Bollman and Mann indicated that hypertrophy of the remaining kidney after nephrectomy is greatly increased by the accumulation of urinary products in the blood following transplantation of the ureter into the duodenum.

It is thus evident that this is a complex problem requiring additional investigation. Experimental research indicates the simplest procedure from the surgical standpoint, accompanied by but few alterations in the constituents of the blood (which may be corrected by diet and medication) is diversion of the urinary stream into the rectosigmoid.

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EARLY CORRECTION OF CONGENITAL CHORDEE AND HYPOSPADIAS

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Few operations have been fraught with more disappointments than the repair of severe chordee and hypospadias. Since 1935 we have participated in the attempted correction of a large number of such cases, have run the gamut of operative procedures and have shared the headaches and heartaches of postoperative fistulas, strictures, infections and bizarre deformities.

Our results during the past 4 years with an operation devised by Cecil have prompted an enthusiastic endorsement of this 3-stage procedure. Absence of postoperative complications and the adaptability of the technique to patients of all ages have made it our operation of choice.

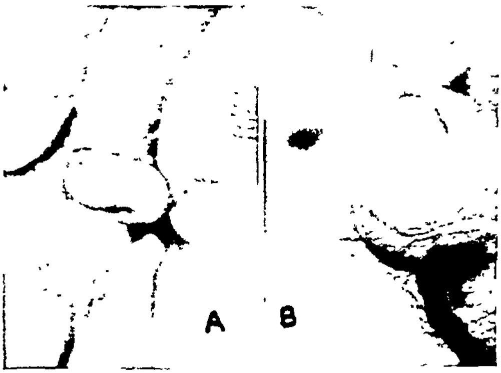

FIG. 1. Typical severe chordee and hypospadias. *A*, child. *B*, young adult.

Mild hypospadias without chordee should not be disturbed during childhood and seldom requires operation in adult life. Cabot insisted that this type should be treated with "masterly neglect." The 24 patients included in this report had sufficient chordee to preclude any semblance of normal coitus. As shown in figure 1, some type of correction is obligatory in such cases.

Satisfactory straightening of the penis must precede any attempt to provide additional urethra but some surgeons have not been impressed by the importance of this step. O'Conor reported "16 patients who had so much penile deformity which persisted after a good reconstruction of the urethra done elsewhere that marriage was impossible." We are convinced that even experienced operators occasionally will be dissatisfied with the result of the original straightening and will want to repeat this stage before constructing the new urethra. This was true in 2 of our 24 cases. Correction of the chordee should not be combined with the urethroplasty but should be a separate procedure.

Read at annual meeting, American Urological Association, Washington, D. C., May 29, 1950.

Pettit found atrophy of the cells of the corpora cavernosa along the ventral surface in a child of 10 years. This probably accounts for imperfect straightening in some young adults despite thorough excision of the fibrous bands. We prefer to correct chordee during the first 2 years of life but, unfortunately, only 6 of our 24 patients were available at that age.

Several 1- and 2-stage operations have been devised for correcting chordee. A few include ingenious redeployment of the hooded prepuce to provide ample skin for the urethroplasty. We have continued to use a very simple method that was popularized by the late Hugh Young.

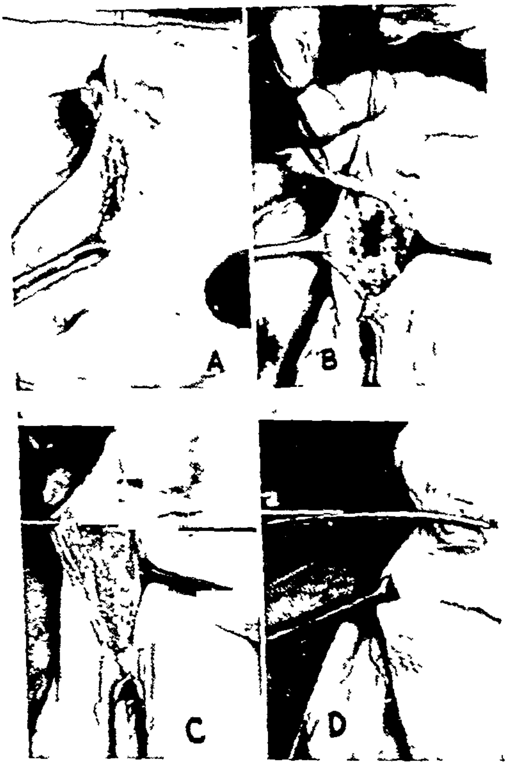

FIG. 2 First stage correction of chordee *A*, terminal urethra freed from corpora. *B*, incision extended, lateral flaps undermined, fibrous band being excised from groove between corpora *C*, freeing of hooded prepuce. *D*, right angle incision into prepuce to provide additional ventral skin.

FIRST STAGE

With a silk traction suture in the glans penis, the hypospadiac meatus is circumcised and the terminal 1 or 2 cm. of the urethra are freed from the corpora (fig. 2, *A*). Not infrequently the meatus is constricted and must be split to insure an adequate lumen.

The ventral surface of the penis is incised from the denuded area to the glans; the skin is freed laterally and all of the fibrous tissue is removed from the groove between the corpora (fig. 2, *B*). The importance of thorough excision cannot be over-emphasized. Accidental defects in the corpora can be repaired easily with fine plain catgut and do not jeopardize the final result in any way.

Ample ventral skin is provided by right angle incisions into the freed hooded prepuce (fig. 2, *C* and *D*). More complicated maneuvers are not necessary if circumcision has been avoided.

The elongated skin flaps are brought together with end-on-mattress sutures of fine tantalum wire. The urethral meatus is allowed to retract to its most convenient position, usually near the penoscrotal junction, where it is anchored with similar suture material (fig. 3, *A*).

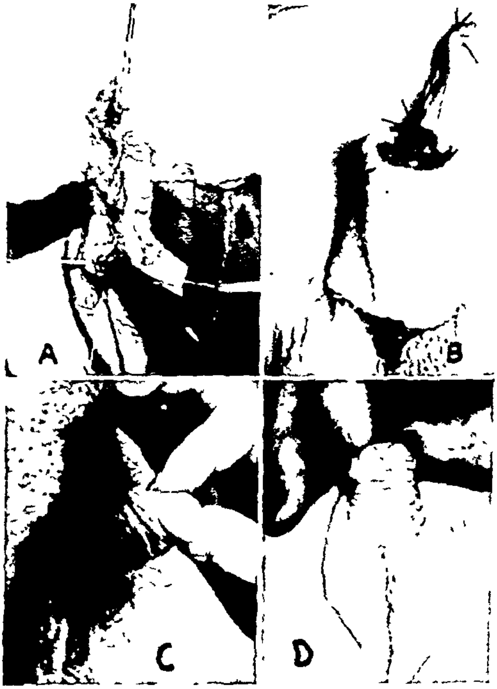

FIG. 3. First stage, continued. *A*, elongated skin flaps closed with fine wire sutures. Note added length and meatus at penoscrotal junction. *B*, elastoplast dressing and rubber traction to lower abdominal wall. Meatus exposed. No catheter. *C* and *D*, typical results 2 months after straightening. Meatus at penoscrotal junction *C*, young adult *D*, child.

Marked edema was common after this operation until we adopted an elastoplast dressing (fig. 3, *B*). Catheter drainage is unnecessary but the meatus must be left exposed. The original deformity is over-corrected by attaching the traction suture to the abdominal wall for 5 or 6 days (fig. 3, *B*).

In children a short anesthetic simplifies removal of the wire sutures 10 days later. Wire produces minimal scar tissue and has shortened the necessary interval before construction of the urethra. The ventral skin usually is soft and pliable in 2 months (fig. 3, *C* and *D*).

There is very little agreement regarding the ideal time for construction of the new urethra. We contend that it is the inalienable right of every boy to be a "pointer" instead of a "sitter" before he starts to school. Since Michigan provides public kindergarten, we have constructed many urethras when the patients were 4 or 5 years of age. It is hoped that our results will help to refute any claims that operations at this age are too difficult or unpredictable.

Some surgeons may question our conviction that it is a major catastrophe for a school boy to have to sit down to urinate, but it is difficult to ignore the enthusiasm with which 5-year-olds announce that they no longer pass urine like their sisters, or the pathetic adolescents who change clothes at the gymnasium and swimming pool in secluded corners because of personal embarrassment, or the inferiority complexes of young adults who are concerned about their marital futures. The psychic trauma to parents may be even more disconcerting. Let any "Doubting Thomas" outline the time schedule he would prefer for his own unfortunate son!

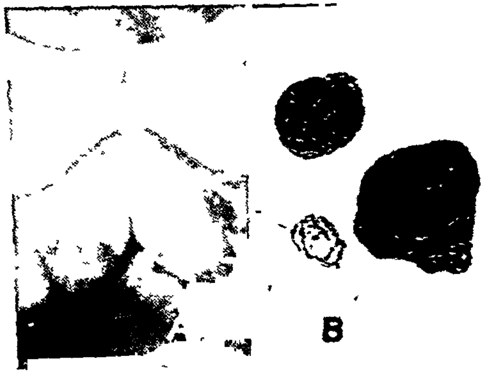

Fig. 4. Calculi that formed in nest of hair after Ombrédanne operation

Many operations have been proposed for construction of urethras but most have been merely modifications of a few basic principles. Success with some methods would seem to be the result of Divine Providence rather than technical achievement. The 3 most popular types of reconstruction have been: 1) variations of the Thiersch-Duplay technique, 2) the Ombrédanne operation and 3) free tube grafts.

Tube grafts have been especially valuable in adults but the consensus of opinion is that they should not be tried before puberty. Havens thinks that the best age is 16 years. F. Young and Benjamin have reported excellent results in 16 preschool patients but 11 of their group had some degree of postoperative urinary fistula. We find postponement of operation for as long as 14 years and a high incidence of fistula (large or small) most objectionable.

Freedom from fistula of the Ombrédanne operation has been overshadowed by hair within the urethra, calculi and excessive dribbling from the pouch-type of urethra. Preliminary depilatory procedures have not eliminated the hairs and their sequelae. Figure 4 shows 2 urethral calculi that formed in a nest of hair despite 4 preoperative electrolytic depilations.

The Thiersch-Duplay principle has been sound but stalked by a high incidence of postoperative fistula. Urethras constructed of inverted penile skin have grown with the penis. Hairs, calculi and weird deformities have been avoided but at least one fistula has been the rule (fig. 5). Repairing them has not been easy. The small one shown in figure 5, *B* required 4 additional operations. Any fistula can be ignored much more easily by the surgeon than by the victim. Regardless of the alleged simplicity of manually closing such openings during micturition, we have been unable to derive any satisfaction or consolation from teaching these patients the fundamentals of piccolo playing.

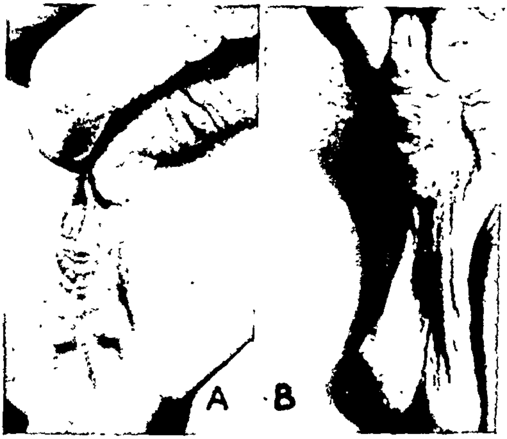

FIG. 5. Fistulas after Thiersch-Duplay urethroplasty. *A*, large, through which all urine passed. *B*, small, but 50 per cent of urine escaped.

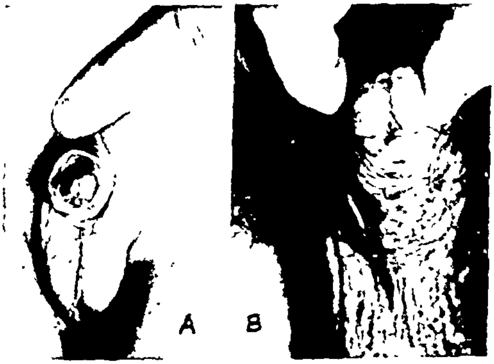

FIG. 6. Meatus at frenum 2 months after final operation. *A*, child. *B*, young adult.

In the 1936 edition of Cabot's *Modern Urology*, Cecil published a modification of the Bucknall operation. Cabot reported the same operation at a staff meeting of the Mayo Clinic during the previous year but added "if any question of priority should arise, it would belong in my judgment to Cecil." The new urethra was constructed by the Thiersch-Duplay technique, buried in the scrotum and released at a later stage. In 1940, Davis mentioned that he had used the same method to cure a patient in 1922.

We have used Cecil's operation (with slight modification) for constructing the urethra in 19 of our patients. It has eliminated fistulas entirely and has retained all of the commendable features of the original Thiersch-Duplay operation.

With any urethroplasty some decision must be made regarding the proposed site of the new meatus. Because of occasional cobra-head angulation of the glans, excessive bleeding in this area, incidence of stricture in glandular segments and possible grotesque distortion of the tip, we agree with Cecil and many others that the urethra which terminates in the region of the frenum (fig. 6) will guarantee the best end result. This location permits excellent direction of the urinary stream, as *demonstrated* by figure 10.

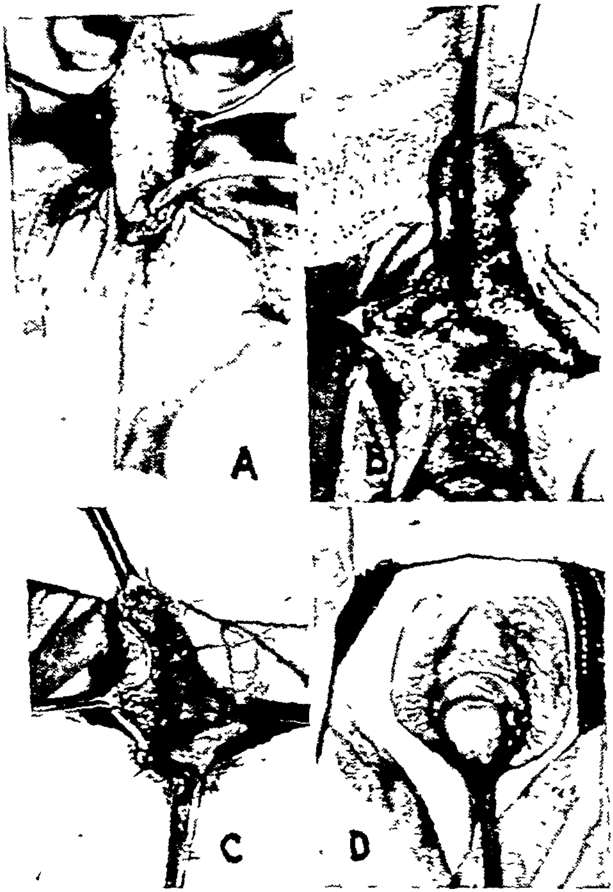

FIG. 7 Second stage construction of urethra. *A*, parallel incisions joined back of meatus. *B*, medial skin sutured over urethral catheter; corresponding incision in scrotum; lateral flaps freed. *C*, corpus cavernosum sutured to deep scrotal tissue. *D*, burial of urethra and ventral surface of penis in scrotum completed with subcuticular sutures. Indwelling catheter anchored with original traction suture.

SECOND STAGE

With a traction suture in the glans, parallel incisions are made on the ventral surface and joined just back of the displaced meatus (fig. 7, *A*). The lateral skin flaps are undermined and the edges of the medial strip are approximated over a 10F or 12F catheter (larger if adult) with a continuous Lembert-type suture of 00000 plain catgut (fig. 7, *B*). Special care is necessary near the end to avoid tension on the suture line and possible subsequent retraction of the new meatus.

A midline incision is made in the scrotum and the skin is freed laterally until there is no dimpling at the penoscrotal junction (fig. 7, *B*). If it has been necessary to construct new urethra from the middle of a bifid scrotum or from the perineum, a layer of deep scrotal tissue is interposed to cover the scrotal segment of the new channel. The penis is buried in the scrotum with interrupted 0000 chromic catgut sutures in the deep tissues (fig. 7, *C*) and continuous 00000 plain catgut in the subcuticular zone (fig. 7, *D*).

Cecil diverts the urine by way of perineal urethrostomy. This was employed during the second stage in our earliest cases but has been abandoned with no ill effects. The indwelling urethral catheter is anchored with the silk traction suture (fig. 7, *D*) unless the new urethra is of sufficient caliber to accomodate a self-retaining Foley catheter. Most catheters have been removed on the seventh postoperative day.

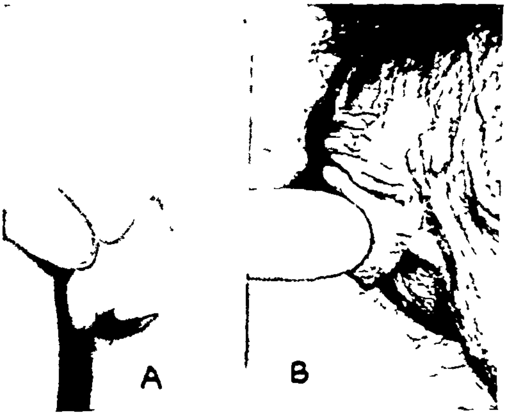

FIG 8. Two months after second stage. *A*, child. *B*, young adult

In 3 of our 19 cases, urine escaped from some point along the skin closure after removal of the catheter. In each instance the leaking ceased spontaneously during the following week. Cecil has informed us in a personal communication that he has had similar experiences but has had no persistent fistulas. In one adult we even omitted the splinting catheter. Urine sprayed from both sides for several days but within 2 weeks it was passing solely from the meatus. The confusion and worry incident to this bold venture have deterred us from trying it again.

Release of the penis and urethra is easiest after at least 2 months have elapsed. Figure 8 shows the usual appearance at this time.

THIRD STAGE

Incisions are made lateral to the linear scars and are joined near the new meatus (fig. 9, *A*). We have left a strip of scrotal skin attached to the penis on each side but in most cases we have been able to remove these strips and effect a final closure with penile skin only, providing the latter has been freed laterally.

The urethra is identified easily by passing a filiform-tipped, woven catheter (fig. 9, *B*). Special precautions are taken to preserve the integrity of the new urethra during the freeing but the dissection must be carried to the base of the penis (fig. 9, *C*).

The skin of the penis and scrotum is closed with fine tantalum wire (fig. 9, *D*). Catheter drainage is unnecessary. The sutures are removed after 8 days and there have been no late complications. Figures 10 and 11 show some of our results.

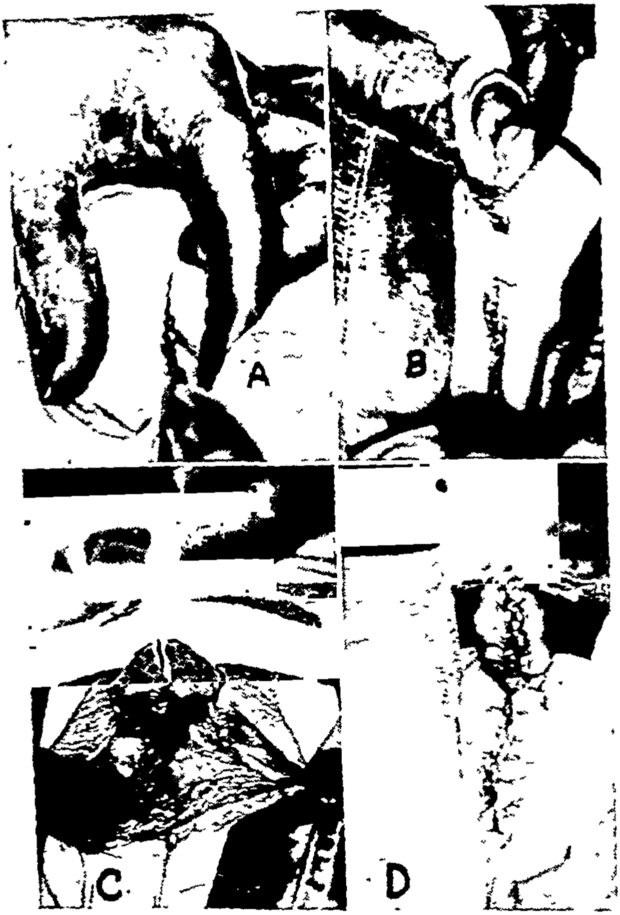

FIG. 9. Third stage release of penis and new urethra. *A*, incision in scrotal skin lateral to old scar. *B*, similar incision on opposite side joined distal to new meatus. Catheter inserted for identification of urethra during dissection. *C*, freeing penis and urethra towards penoscrotal area. *D*, skin closed with fine wire sutures. Catheter is removed.

In a few instances, our conservation of penile skin may necessitate later circumcision.

Small doses of antibiotics are given during each stage. All patients who have passed puberty also receive diethylstilbestrol to prevent erections during convalescence.

Table 1 summarizes 5 patients who had from 2 to 9 unsuccessful operations before this type of repair affected complete cure. One of these still had some chordee and required further straightening.

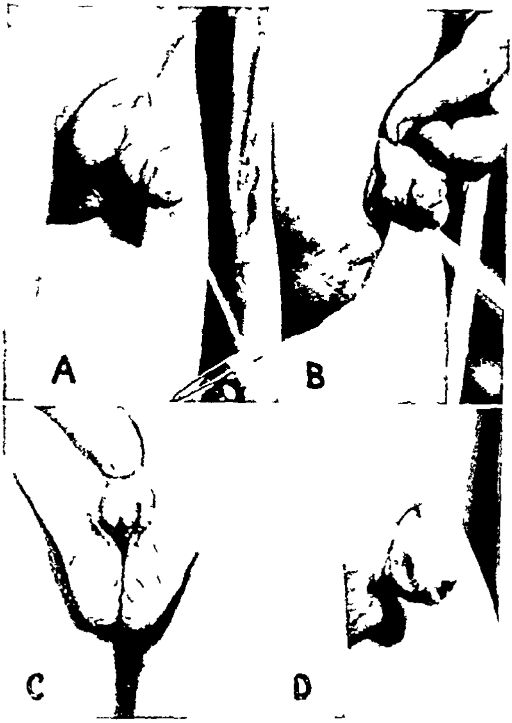

FIG 10 *A* and *B*, final results in 2 preschool patients Note direction of urinary stream *C*, preschool patient before first stage *D*, after third stage

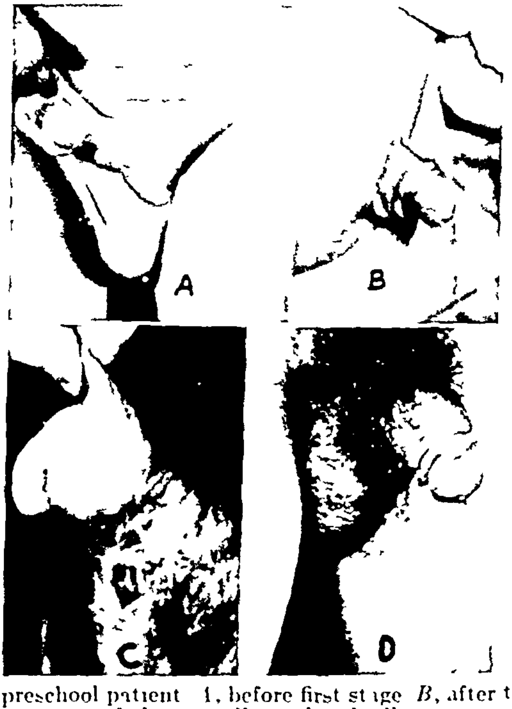

FIG 11. *A* and *B*, preschool patient *A*, before first stage *B*, after third stage *C* and *D*, young adult *C*, after 9 previous failures Still angulated, all urine passed by way of opening to left of midline *D*, after third stage

Table 2 summarizes the 14 patients who were spared such failures. One young adult required 2 operations for correction of his chordee. The hypospadias was penoscrotal in all but 2 cases. All of the patients were cured with the Cecil operation.

Ten of our 19 patients were cured by the time they were 6 years of age. The others were victims of procrastination and misdirected efforts.

TABLE 1. *Five failures after other types of urethroplasty*

NO	NUMBER OF PREVIOUS PLASTICS	RESULT		CECIL OPERATION			AGE WHEN CURED
		Straight	Meatus	Stage 1	Stage 2	Stage 3	
1	2	yes	penoscrotal	not nec.	1947	2 mo. later	6
2	2	yes	prox. shaft	not nec.	1947	2 mo. later	8
3	6	yes	midshaft	not nec.	1949	2 mo. later	16
4	9	no	penoscrotal	1948	1949	2 mo. later	21
5	4	yes	penoscrotal	not nec.	1949	2 mo. later	34

TABLE 2. *Fourteen patients without previous urethral surgery*

NO	STRAIGHTENING		RESULT	LOCATION OF MEATUS	CECIL OPERATION		AGE WHEN CURED
	Age	Year			Stage 2	Stage 3	
1	3	1946	straight	penoscrotal	1947	1 mo. later	4
2	3	1949	straight	penoscrotal	1949	4 mo. later	4
3	2	1948	straight	penoscrotal	1950	2 mo. later	4
4	2	1944	straight	penoscrotal	1946	2 mo. later	5
5	2	1944	straight	penoscrotal	1947	2 mo. later	5
6	4	1946	straight	penoscrotal	1947	1 mo. later	5
7	4	1947	straight	penoscrotal	1947	4 mo. later	5
8	4	1949	straight	scrotal	1950	2 mo. later	5
9	6	1948	straight	penoscrotal	1948	2 mo. later	6
10	6	1945	straight	penoscrotal	1947	4 mo. later	8
11	4	1941	straight	prox. shaft	1949	10 mo. later	13
12	11	1945	straight	penoscrotal	1946	13 mo. later	13
13	16	1948	straight	penoscrotal	1949	4 mo. later	17
14	26	1946	repeated 1947	penoscrotal	1947	1 mo. later	27

Five additional patients have had their chordee corrected but are still awaiting urethroplasties because all 5 are less than 4 years of age. One of these is of special interest since he was considered a girl at birth (fig. 12, A). There were 2 scrotal sacs, an interposed recess that resembled vagina, a diminutive phallus and a large, hollow, red mass to the right of the anus that seemed to be a vestige of cloaca. The urethra opened deep in the vagina. A cervix or prostate could not be demonstrated.

At 6 months of age the red mass was excised, the pelvis was explored and no female organs were found. Biopsy of the gonad in each scrotum revealed testicular tissue. His name was changed and 1 year later the so-called vaginal mucosa was used to construct urethra to the base of the small penis, after which the scrotums were joined. The status of this child at 2 years of age is shown in figure 12, *B*.

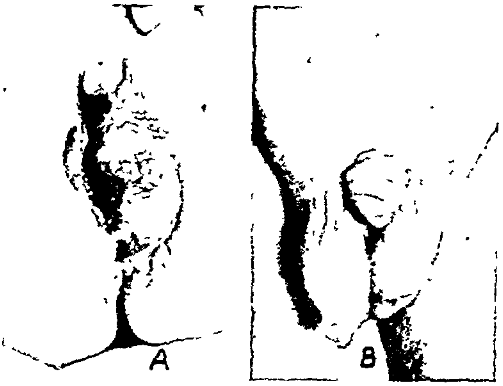

FIG. 12. Male pseudohermaphrodite. *A*, at birth. *B*, after excision of vestigial cloaca, construction of part of urethra and joining the 2 scrotums.

SUMMARY

Because of 1) the absence of postoperative fistulas, urethral hair, strictures and bizarre deformities, 2) the adaptability of the operation to patients of all ages, 3) the precise number of necessary surgical procedures and 4) the consistently excellent functional results, we urge more general utilization of the Cecil operation for curing hypospadiacs before they start school.

Mayo Clinic, Rochester, Minn.

REFERENCES

CABOT, H.: An improved operation for hypospadias. Proc. Staff Meet. Mayo Clinic, **10:** 796, 1935.

CABOT, H.: The treatment of hypospadias in theory and practice. New England J. Med., **214:** 876, 1936.

CECIL, A. B.: In Modern Urology, edited by Hugh Cabot. Philadelphia: Lea and Febiger, 1936, 3rd ed.

CECIL, A B.: Repair of hypospadias and urethral fistula. J. Urol., **56:** 237, 1946.

DAVIS, D. M.. The pedicle tube-graft in the surgical treatment of hypospadias in the male. With a new method for closing small urethral fistulas, Surg., Gynec. & Obst., **71:** 790, 1940.

HAVENS, F. Z.. Hypospadias (editorial). Surg., Gynec. & Obst., **87:** 239, 1948.

O'CONOR, V. J.: In discussion of McKenna, C. M., Hypospadias, observations on its surgical correction. J.A.M.A., **113:** 2143, 1939.

PETTIT, J. L.: Quoted by Cecil, A. B., Surgery of hypospadias and epispadias in male. J. Urol., **27:** 514, 1932.

YOUNG, F. AND BENJAMIN, J. A.: Preschool age repair of hypospadias with free inlay skin graft. Surgery, **26:** 384, 1949.

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DISCUSSION

DR. DONALD A. CHARNOCK (Los Angeles, Calif.): Dr. Culp is to be commended for this report on his work with the trying problem of hypospadias. Fifteen years of effort in this field should qualify him for a medal for bravery, above and beyond the call of duty. Dr. Culp is further to be commended for experimenting with the various methods of repair and finally deciding upon the one technique he thought most suitable and mastering this. Fourteen cases completed in 4 years is a commendable record.

I quite agree that mild hypospadias, without deformity, should not be tampered with. I also agree that a thorough excision of the fibrous material which, in my opinion, is the cause of the deformity of chordee, is the most important and often the most difficult step in curing hypospadias. I have no hesitation in repeating the correction step if chordee is still present.

The skin defect in the shaft, resulting from this dissection, may be closed in several ways. In the Bucknall-Cecil operation a simple closure along the axis of the shaft is quite satisfactory. Where a Thiersch-Duplay type of procedure is being used to construct the urethral canal, a broader base is necessary. For this we use the prepuce as a hood thus securing a broad base for our construction of the urethra.

With all respect to Dr. Davis, Dr. Benjamin and others, who employ ingenious tube grafts in order to bring the urethra to the tip of the penis, we are quite content to end the urethra at the level of the glans. We believe this gives a functional penis without danger of stricture formation.

Dr. Cecil's operation is excellent. It is much safer than the Thiersch-Duplay types of procedures. We have been using the latter over a period of years in an attempt to evaluate this type of closure. As Dr. Culp has pointed out, the Ombrédanne operation is not surgically correct.

It is my opinion that whatever type of operation is used, it should be done in definite steps with sufficient time between each step to insure healing and softening of the tissue. Several months between each step is necessary to allow the penile skin to properly heal.

I have never been impressed with the necessity of completing the operation at an early age. I believe the straightening step should be done before school age. The construction of the urethra should be completed before puberty. In the boy of 8 or 10, we get much better cooperation. At this age the skin is easier to handle. More of it is present. I still believe we are able to cut a better garment if we have more cloth.

I believe that the angle of psychic trauma has been much overemphasized. Much of this problem comes from the mothers. I find them cooperative when they understand the program. I always explain the entire problem fully to the parents. We teach our boys to stand up to void after the first stage. If they have any trouble with their little friends, we teach them to lead with their left.

DRS. JOHN A. BENJAMIN AND FOREST YOUNG (Rochester, N. Y.): We should like to present our study and experience with a 2-stage procedure, one to correct chordee and one to reconstruct the urethra in 32 cases, which started *9 years ago.* The chordee has been corrected in 32 cases, and the urethral reconstruction has been completed in 25, of which 17 left the hospital healed. But what we believe is more significant is that the last 9 consecutive cases, in the group of 17, left the hospital completely healed and urination was very satisfactory. Hence there is good reason to believe that our procedure for urethral reconstruction, the basic principles of which were introduced by Nové-Josserand in 1897, is standardized to the extent that it can be depended upon to yield very satisfactory results.

We would like to stress the following points in regard to the procedure:

1) Use for any degree of hypospadias, recommending Ombrédanne procedure for minor degrees of hypospadias.

2) Place the urethral orifice off to one side of midline at the time the chordee is corrected about 1 year of age.

3) Reconstruct the urethra with a free inlay skin graft about 2 to 3 years of age. Before the urethra is anastomosed to the graft cut off the part of the urethra, that is dilated or traumatized. Two layer closure (subcutaneous tissues and skin) at site of anastomosis with interrupted 0000 chromic catgut.

Some advantages of this procedure are: a) two stages; one to correct chordee and one to reconstruct urethra in preschool age children; b) urethra opens in glans; c) lack of hair; d) lack of multiple fistulas; e) erections no problem; f) minimal number of urethral dilatations; g) surgical procedures and hospital stay are for short periods of time.

Dr. Harry M. Spence (Dallas, Texas): I want to emphasize what Dr. Culp said about the most important part of the whole job being correcting the chordee. That is the sine qua non of getting a good looking, functional penis. I have tried the simple operation of just dividing transversely the fibrous bands which represent the rudimentary corpus spongiosum, and closing the incision longitudinally, and it has not worked well in my hands. I have tried the more extensive procedure of Cabot that he showed and it works better, but I do not think it is quite so good as the way that Dr. Nesbit has devised for straightening the chordee. I would like to show some slides of that, please.

(Slide) This is a 12-year old boy, and shows the deformity. He had not been circumcised. One cannot use this technique if the patient has been circumcised.

(Slide) Here a circular incision is made just proximal to the corona, completely around the penis, and the skin is denuded entirely along the entire penile shaft. I carry this incision completely down to the corpora cavernosa.

(Slide) Here you see how completely the penile shaft has been denuded.

The next thing is to develop the two layers of natural foreskin into a single layer and bring the glans through a button-hole in the single sheet of tissue.

(Slide) This has been done there. The little area down below represents the original incision being closed transversely and the buttonhole sutured back of the glans.

I leave a catheter in for a couple of days, although it is not essential.

As for the bleeding of this operation, as someone said about the retropubic operation, the sooner you learn to disregard it, the better you will get along. When I get through, I put on a pressure dressing.

(Slide) This is the first dressing after approximately a week. Notice the abundance of hair-free, pliable skin that is available for any type of operation you want to do later on; (slide) and there it is 6 months later, just before starting the second stage. I think you will agree that he has come a long way.

I will not describe the second stage that we do. It is essentially the original Duplay technique, using stainless steel wire suture.

Dr. Robert Moran (Washington, D. C.): I feel that it is a great honor to be allowed to speak before this distinguished gathering. Not being a urologist, you will have to bear with me.

I have come into these cases accidentally, and I want to congratulate Dr. Culp on his wonderful results.

In doing these operations, after the patients have been operated on several times, knowing the poor results on this type of procedure, we have had to shift to many types of operations. In the first group of cases, where we get the patients before surgery has been done, and where the chordee is marked, I have added one little step: I have placed the tip of the penis under the abdominal wall. I have had six of these cases and they have overcorrected the deformity. None of them have had any complaints and none have reached the masturbation age or any age where trouble might result.

There is one point I would like to make that may fit in with Dr. Culp's operation. I believe that in all plastic procedures, we should avoid a straight suture line. A straight suture line will always contract and, in two pedicle flaps recently, I found, by a little shift and having a spiral type of incision or a spiral type of wound, we do away with any longitudinal contraction.

I may be able to show it with a diagram. I have used two blades on a knife and we can gauge and separate the blades at any distance we want, from 1 to 2, to 2½ cm. This being the urethra (the diagram does not show clearly what I want to convey), we have a spiral curve, like a snake's tail, and when we turn those over, either catheter or free, we have a spiral incision, and in none of the cases, other than in the urethra, have I had any contraction at all.

I have 2 cases in which I am going to try this. We can do the second and third steps, according to Dr. Culp, and then even have a spiral or curved incision.

In the free graft, I also think instead of having a straight line where the suture is brought together, if you have that spiral, I am positive, in doing that type of buried graft, that we do get contracture along the suture line.

Dr. Ormond S. Culp (Detroit, Mich.): It is a foregone conclusion that somewhere in the audience is a champion of practically every type of operation that has ever been reported, otherwise, the procedures wouldn't be in the literature. I still claim that, sooner or later, we will all revert to as simple an operation as possible, and I think Dr. Cecil has paved the way for that.

If we are going to correct these hypospadiacs early in life, we might as well do it before the patients start to school rather than at some later age.

I have two objections to Dr. Benjamin's work. In the initial report there were fistulas in 11 of the total 16 cases. I hope he doesn't have any more, but I think this type of operation is destined to be fraught with an undesirably high incidence of fistula.

With due respect to Dr. Moran, my second objection is that the operation is being done by the plastic surgeons and not by urologists.

Dr. Spence has been impressed by the Nesbit operation for straightening. So have I. Many years ago Dr. Creevy said if you simply remove all scar tissue, you can redeploy the skin any way you wish. The more complicated redeployments of the skin are scarcely necessary if the patient hasn't been circumcised.

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HYPOSPADIAS: A CONCEPT OF TREATMENT

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The development of a concept of treatment for the more serious degrees of hypospadias directed toward elimination of the common complications requires a basic knowledge of standardized procedures. About such an often discussed subject there can be little that is entirely new. Even the uninitiated must realize however that the vast number of reports is but an indication of continued inadequacy.

The historical record has been amply reviewed by Cecil and others with the proper assignment of initial credit for the generally standardized treatment methods. A survey of the extensive literature amply indicates that very few if any technical ideas appear to have been left untried. The inference that any conception of operative procedure may be considered entirely new is apt to prove erroneous.

Having the not uncommon experience of producing a number of often partially satisfactory results an attempt was made to analyze the difficulties encountered. A deliberate effort was made through a series of sketches and models to overcome these problems. Previous efforts directed toward correction of chordee often suffered from a too timid and limited approach. The length of the urethra produced seldom seemed completely adequate and rarely equalled expectations. Fistula formation, particularly in lesions of advanced degree, has always been an annoying problem. Maintenance of adequate drainage despite the method used occasionally fails when most needed.

Numerous versions of hypospadias treatment successfully utilize the prepuce in various ingenious ways. The principle of a urethra formed in part by preputial tissue was devised by Van Hook in 1896. Among the numerous variations the reports of Mayo, Russell, Donnet, Davis, Kieffer, and others clearly indicate the variety of means afforded by the use of this tissue. Its use does not, as suggested by Cecil in his exhaustive survey, appear to particularly complicate the problem. Preputial skin when properly utilized proves quite elastic and pliable. This has been demonstrated in the author's method of treating epispadias in which the prepuce adequately supplied tissue for the entire urethra without tension.

Correction of chordee when severe has not previously been entirely satisfactory and the decision was reached that complete or nearly complete denudation of the penis was necessary in many instances for release of constriction. Use of preputial tissue with a rearrangement of penile integument, in a manner similar to that reported by Nesbit, seems logical.

The problem of adequate continuous diversion of urine has been given careful consideration. Either perineal or suprapubic drainage is adequate, provided function continues. Obstruction may occur however at the most inopportune time as the result of amorphous deposits despite considered prophylactic measures. Not infrequent is the experience of a tube forcibly removed by the patient or careless attendant. Though replacement is often only an annoying problem, considerable damage may have resulted in the interim. The employment of a nephrostomy tube with attached nonperforated ureteral extension seems logical. Such a catheter provides ample drainage in addition to a mold about which the urethra may be constructed. Should the occasion arise, irrigation or two way drainage may be instituted thus serving the purpose, as suggested by Cecil, of combined abdominal and perineal drainage. In addition this apparatus serves as an easy means of introducing a new catheter should the need arise.

In most accepted procedures for advanced degrees of hypospadias, constriction at the penoscrotal juncture is apt to occur resulting in fistula or stricture. Such a possibility may be overcome by use of parallel incisions through skin and fascia.

METHOD

The method evolved has been used in varying grades of hypospadias, chiefly in advanced penile and penoscrotal types, but appears to have advantages applicable to any degree of deformity. In the more advanced conditions the two stage procedure is generally advisable. The first stage involves the release of chordee, formation of the glanular urethra and provision for very ample tissue for the subsequent employment of the Thiersch-Duplay technique or other desirable method. Of essential importance in correction of chordee is a very bold approach and the method employed requires a nearly complete denudation of the penis with an almost total rearrangement of integument which is made possible by the use of a pedicle flap developed from the prepuce. This simultaneously allows formation of the glanular urethra and abundant tissue for the subsequent formation of the penile urethra. Length of flap obtained has been sufficient in all instances of penile lesion and most cases of scrotal hypospadias.

Careful preparation of the operative site is important. In recent cases detergent surgical soap preparation has been used with apparently good results and appears to have advantages over more irritating preparations especially in the very young. With the penis extended the initial incision is begun at the urethral orifice and extended in the form of a narrow V-shaped wedge to a position immediately proximal to the glans. A wedge of skin and the underlying intercavernosal septum is deeply and widely excised sufficient in degree to allow a maximum of unrestricted extension of the penis (fig. 1). This is generally not completely satisfactory for the correction of chordee. Therefore a skin incision is carried around the corona leaving a narrow margin of penile shaft skin attached to the glans. Bold denudation of the penis is then carried out by blunt dissection with due respect to the vascular supply, separating the skin from the underlying fascia. Thus one large hood like flap is formed attached only about the proximal portion of the penis but varying according to the need determined by the degree of initial deformity. This procedure is similar in some respects to the method described by Nesbit and others and is important if complete correction of chordee is to be obtained (fig. 2).

The double layered prepuce is placed under tension and is separated according to established principle by incising along the lateral borders beginning at the previous penile encircling incision (fig. 2). Detailed attention to the maintenance of all possible blood supply is mandatory. Of essential importance is an understanding that the resultant flap is quite elastic and will afford considerably more useful integument then might be anticipated. An estimate is then made of the skin required to cover the dorsum of the penis without undue tension and yet afford a maximum length of flap for other purposes. A transverse incision is made at this determined point sufficiently wide to allow the glans to be drawn through. A trap door type flap is then formed by two lateral incisions extending from the transverse incision distally and sufficient in length to provide for subsequent formation of the glanular urethra. The length of this structure should be predetermined by measurement and long enough to extend eventually beyond the tip of the penis. Thus the base of this secondary pedicle flap is located distally and worthy of emphasis is the fact that slough of this tissue has not been encountered (fig. 2).

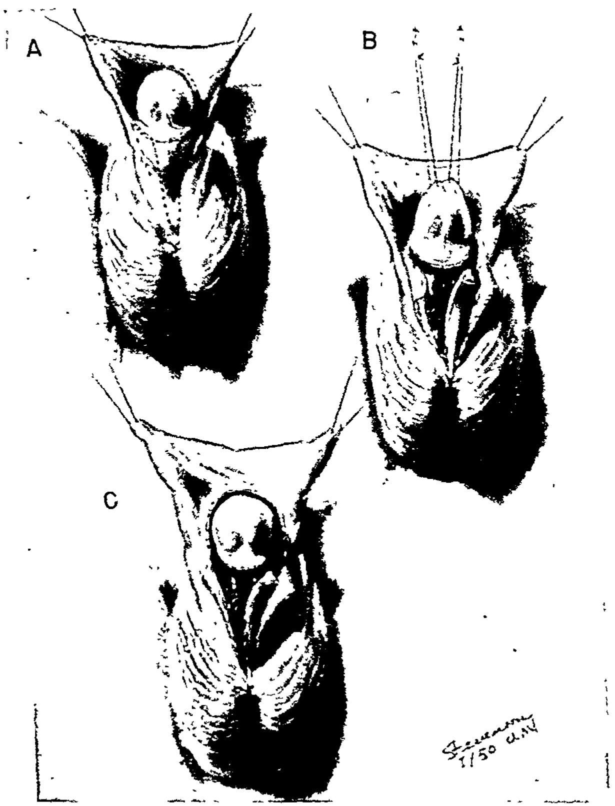

FIG. 1. *A*, line of initial incision. *B*, wedge of skin and intercavernosal septum is deeply excised. *C*, incision extended around corona with a short cuff of skin remaining attached to glans.

The glans is pierced from a proximal position well between the partially as the result of amorphous deposits despite considered prophylactic measures. Not infrequent is the experience of a tube forcibly removed by the patient or careless attendant. Though replacement is often only an annoying problem, considerable damage may have resulted in the interim. The employment of a nephrostomy tube with attached nonperforated ureteral extension seems logical. Such a catheter provides ample drainage in addition to a mold about which the urethra may be constructed. Should the occasion arise, irrigation or two way drainage may be instituted thus serving the purpose, as suggested by Cecil, of combined abdominal and perineal drainage. In addition this apparatus serves as an easy means of introducing a new catheter should the need arise.

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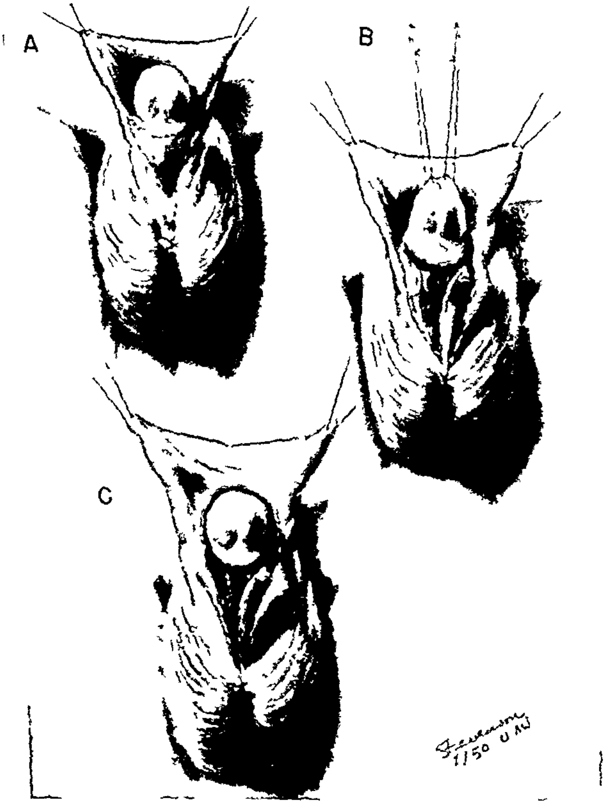

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The glans is pierced from a proximal position well between the partially separated cavernosal bodies to the normal and desired position at the tip of the glans. This canal should be enlarged by the use of a hemostat to provide very ample space for the subsequent passage of the epithelial tube forming the glanular urethra. Subsequent constriction of the urethra at this point has not been encountered and is not a detrimental factor. The glans is drawn through the three sided flap incision and the distal portion of the urethra is formed by approximating the edges of the flap meticulously with interrupted sutures of 0000 or 00000 chromic atraumatic catgut. A short rubber tube serves as a mold which may vary in size according to the patient's age yet small enough in caliber to be freely movable and without exertion of pressure on the newly formed urethra. The pedunculated tube is then drawn through the glanular canal to a position extending slightly beyond the tip of the glans. Two fixation sutures are used to anchor the urethra in place at the tip of the glans (fig. 3).

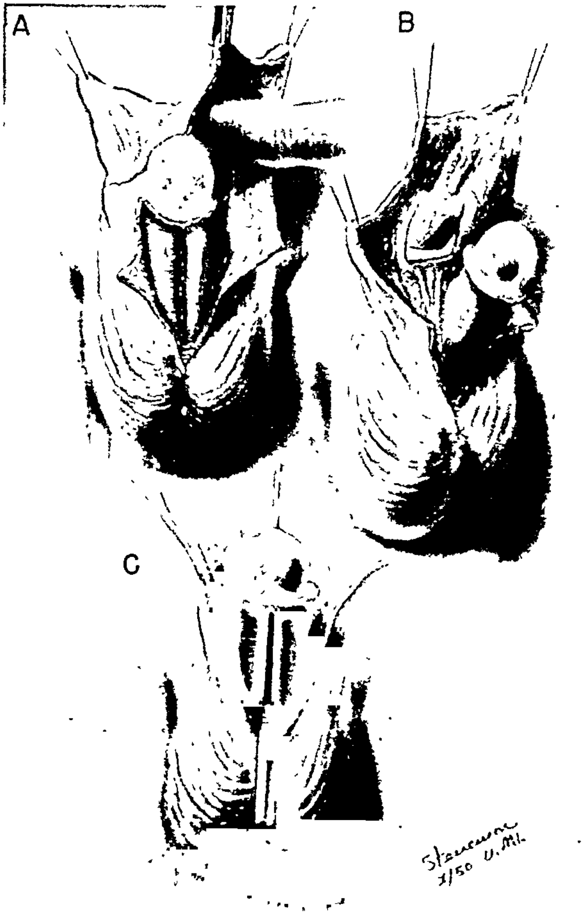

FIG. 2. *A*, development of elastic single layered preputial flap. *B*, formation of trap door flap to be used for glanular urethra. Penile shaft is extensively denuded. *C*, development of glans tunnel.

The penis, partially denuded by the process of correction of chordee, is then covered with the remainder of the dorsally derived flap which is loosely redesigned according to the need. In lesser degrees of penile deformity there is far more than ample tissue available and there has been sufficient preputial skin to reach the urethral orifice in the majority of scrotal hypospadias cases (fig. 3). The excess tissue is excised according to the apparent requirement but without particular

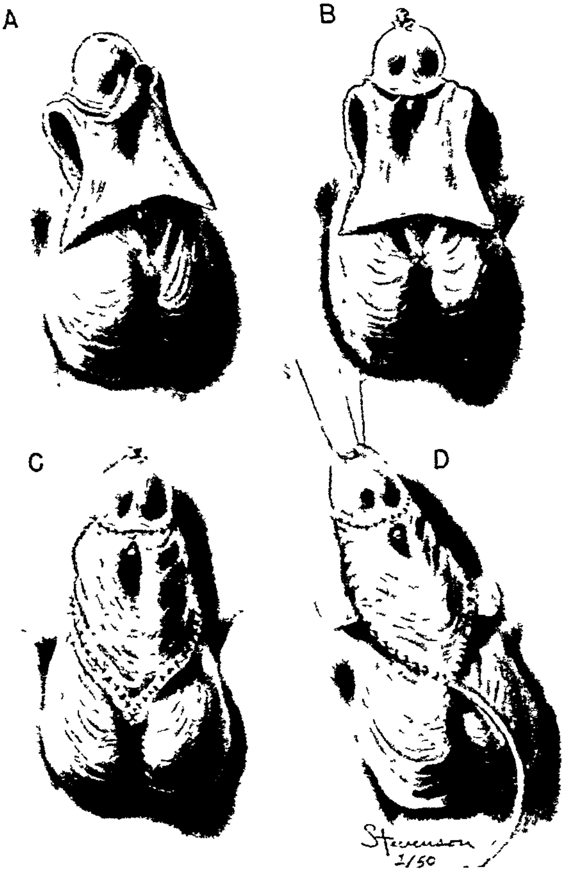

Fig. 3. *A*, preputial flap drawn over glans. *B*, secondary glanular urethra flap developed as a tube and drawn through prepared tunnel. *C*, extended denuded penis covered loosely by approximating elastic flap to retracted penile skin. *D*, completed first stage.

regard to appearance and without sacrifice of possible subsequently needed tissue. Worthy of note is the fact that the large flap completely surrounds the distal portion of the penis and forms the majority of the ventral covering. Specific efforts should be made to provide an appreciable degree of redundant tissue at the point immediately adjacent to the urethra in cases of penile or scrotal hypospadias. Absorbable suture material is used for all skin approximation particularly in young children. Two stay sutures through the glans and the abdominal skin are used to extend the penis over the symphysis. A urethral catheter of appropriate size is inserted and a very light dressing applied. In most instances an ice cap has been used intermittently for the first 24 hours for the purpose of reducing edema and bleeding. In some instances a dry occlusion dressing has been applied but apparently the best results have been obtained by the use of a loose dressing which serves to keep the operative site reasonably clean and is readily changable. Both antibiotic and chemotherapeutic agents have been used

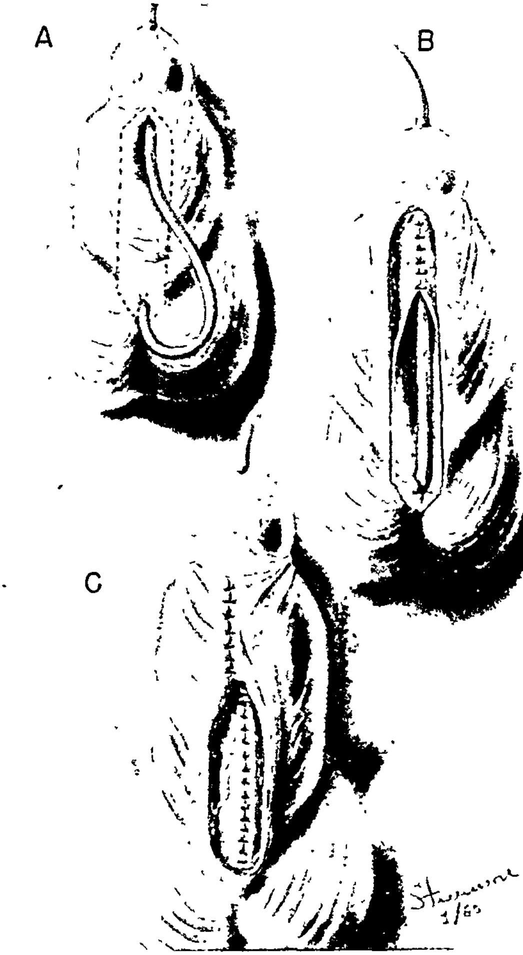

FIG. 4. *A*, line of incision for second stage. Deep intercavernosal groove is demonstrated. *B* and *C*, formation of penile urethra and closure.

empirically. Restraint of most children appears necessary for one or two days and in general the catheters are removed between the fourth and seventh day.

After an appropriate interval, which has varied between 2 and 6 months, the second stage may be done. At this time a well defined gutter may be palpable under the very redundant ventral covering (fig. 4). The urethral canal through the glans has remained patent in each instance and stricture formation has not been encountered. In the majority of instances diversion of the urinary stream has been deemed advisable. Either suprapubic or perineal means may be used and either seems preferable to the use of a urethral catheter only as failure of proper function may too often prove disastrous. Despite all precautions directed toward elimination of anticipated difficulties on occasion both suprapubic and perineal drainage have proved disappointing. Obstruction, despite adequate prophylactic measures and careful observation, has been a common experience as well as the inadvertent or forceful premature removal of the drainage tube. An alternate method was devised which involves the use of a nephrostomy type tube such as the one devised by McIver and others but without perforation in the ureteral portion. Either the balloon or mushroom type may be used (fig. 5). Such a tube provides ample suprapubic drainage and the distal portion serves as a form for the newly constructed urethra. In addition it provides a means for irrigation should catheter obstruction occur. This method may serve the same purpose as combined suprapubic and perineal drainage as described by Cecil; however in the majority of instances we have placed a tie about the urethral portion of the catheter. Though not encountered in this series, one might conceivably wish to pass further urethral instruments and if such is desired attachment may be made and the catheter or instrument drawn through the urethra upon the removal of the suprapubic tube with a minimum of trauma.

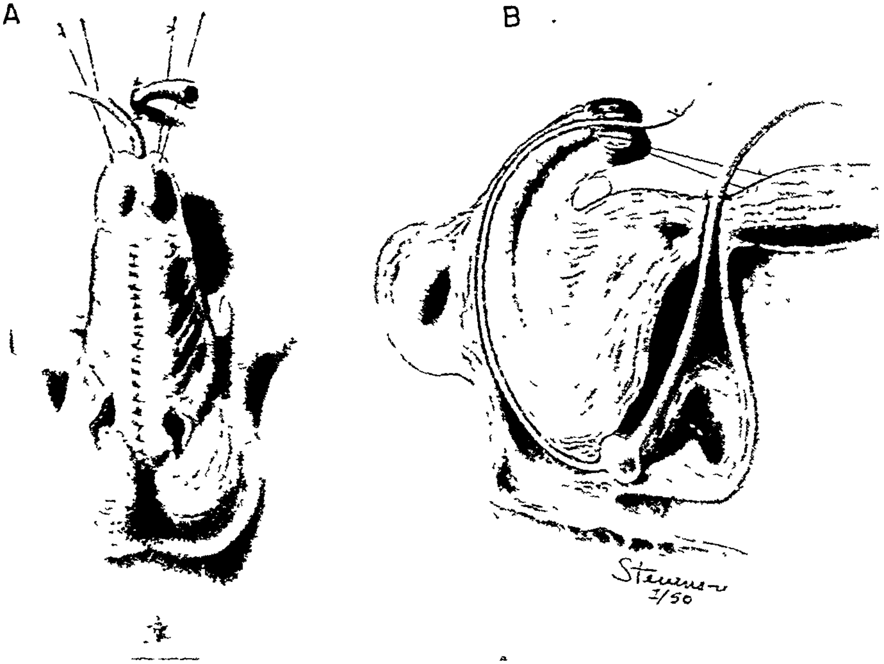

FIG 5 A, tension releasing incisions at penoscrotal juncture, through skin and fascia as required, as aid against fistula formation B, sagittal section showing combination cystostomy and urethral catheter in position suggested as alternate method of drainage

The method of insertion is as simple as a perineal urethrostomy. A small catheter or filiform is inserted through the urethra after the establishment of a very small cystostomy incision. This instrument is secured and drawn through the cystostomy wound and tied or sutured to the tip of the nephrostomy type tube which is then drawn through the urethra from above. Care must be taken to insure that the balloon or expanded portion of the catheter fits snugly at the vesical outlet. The cystostomy tube is then fixed in position by suture to the abdominal wall thus preventing undue motion of the urethral portion while serving its subsequent role.

In each instance the broad ventral pedicle flap previously formed at the first stage has been found to have a very ample blood supply and to be surprisingly redundant and amenable to the formation of the penile urethra. The formation of the remaining urethra has been generally executed along the lines of the Thiersch-Duplay method with but slight modification and closure being accomplished by the use of very closely spaced interrupted 0000 atraumatic catgut sutures (fig. 4). Notable is the fact that there is more than ample tissue available to carry out this procedure without tension with the possible exception of the area immediately at the site of the original urethral orifice. Very particular and careful emphasis should be placed on closure at this position and constriction with tension which is apt to occur must be avoided. The skin should be carefully freed from urethral attachment in the area. Lateral incisions at this possible point of constriction may be used to overcome the possible complication of fistula formation in a manner often employed in plastic surgery. The incisions may be carried through the skin and as deemed advisable into the fascia if the latter seems a constricting factor. This maneuver allows loose approximation of the integument at the juncture of the newly formed urethra and the original orifice. Thus tension which may be evident at the time of operation is overcome (fig. 5). Since edema may develop, particularly in this area, anticipation of such a complication may reduce the tendency to subsequent fistula formation. Only a brief period is required for epithelization of the resultant elliptical defect thus created on either side of the midline. This maneuver seems a simple and ample safeguard against the difficulties commonly experienced in most types of correction.

Stay sutures are placed in the glans and the penis is maintained in dorsiflexion by a small gauze bolster and secured loosely to the abdominal wall. A light gauze dressing only is used and in some instances an ice cap has been applied intermittently for the first 24 hours as an aid in the prevention of edema and a control for bleeding should such occur. The younger patients are restrained for a brief period and the need for careful observation and nursing attention is emphasized. Periodic urinary pH determination may prove quite helpful in the prevention of catheter obstruction but if adequate metabolic balance is maintained such is not likely to occur. The period of catheter drainage is a matter of choice but has been maintained for an average of 7 to 10 days.

SUMMARY

A concept of the treatment of hypospadias has been presented which upon proper execution eliminates the more common complications. Free use is made

of accepted principles and modes of treatment. The method described is particularly applicable in treatment of penile and scrotal hypospadias. Repeated clinical applications have proved satisfactory. Cosmetic and functional results have been good.

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REFERENCES

Cecil, A. S.: Tr. Am. Assoc. G. U. Surg., 24: 253, 1931.
Davis, D. M.: Surg. Gynec. and Obst., 71: 790, 1940.
Kieffer, J. H.: J. Urol., 59: 1169, 1948.
Mayo, C. H.: J. A. M. A., 36: 1157, 1901.
Mays, H. B.: J. Urol., 60: 749, 1948.
Nesbit, R. M.: J. Urol., 45: 699, 1941.
Russell, R. H.: Brit. M. J., 2: 1432, 1900.
Van Hook, W.: Ann. Surg., 23: 378, 1896.

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ALLERGIC GRANULOMAS OF THE PROSTATE GLAND

M. M. MELICOW

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This is the first report of allergic granulomas of the prostate gland. The patient had been suffering from asthma for about one year. Radiographs of the lungs, taken on admission to the Presbyterian Hospital, revealed shadows that were suggestive of tuberculosis. A sudden enlargement of the prostate gland induced symptoms of bladder neck obstruction. It was necessary, therefore, to remove the gland; this was done by the suprapubic route. Sections of the operative specimen showed an unusual lesion which was diagnosed as "allergic granulomas of the prostate gland." Because of this finding, the patient's status was re-evaluated, and he was placed in that group of patients in whom asthma, combined with a pronounced blood eosinophilia, eosinophilic infiltrations in the lungs, scattered allergic granulomas, with or without necrotizing arteritis (periarteritis nodosa), were manifestations of a complex diffuse vascular allergy. The subsequent clinical course and autopsy findings corroborated the diagnosis of allergic granulomas of the prostate gland and of the inference that the prostate was part of a constitutional dyscrasia.

In March 1948, S. H., No. 9101864, a white married man, aged 62, was admitted to the Presbyterian Hospital, because of frequent attacks of asthma of 13 months' duration. The attacks were preceded by a "cold" that had lasted for 6 months, during which time he suffered a profuse nasal discharge. Radiographs of the sinuses revealed "no significant change." An electrocardiograph, taken 2 years prior to his admission to the hospital, was said to be normal. In the last 6 months, however, the patient developed dyspnea, for which digitalis was prescribed. The asthma and the accompanying cough increased in severity in the last month. There were the usual childhood diseases, including pneumonia. Appendectomy was performed in 1918; herniotomy, in 1941. The hernia recurred. He was married for 35 years, and his wife and 3 children were living and well.

On admission, the patient weighed 170 pounds; he had lost 12 pounds in 4 weeks. He was moderately dyspneic. There was some polypoid thickening of the right turbinate and the throat revealed excess lymphoid tissue. The heart was regular, and inconstant sibilant rales were heard in the lungs. The blood pressure was 160/108. A_2 was louder than P_2. The venous pressure was 45 mm., saline (50, 45, 45); a No. 19 needle was used. Skin tests revealed sensitivity to spinach, lobster, celery and powder. Radiographs of the chest (344622), taken on March 8, 1948, revealed small shadows of calcium density in the left upper lung field, which were interpreted as "healed tuberculosis." The heart was slightly enlarged. The sedimentation rate was 25 mm., hemoglobin 15.5 gm., red blood cells were 5,300,000; white blood cells were 14,500, neutrophiles 51, *eosinophiles 26*, lymphocytes 17, and monocytes 6. Bronchoscopy: An 8 mm. bronchoscope was inserted and the entire tracheobronchial tree was found to be markedly thickened. The carina was in the normal position, but appeared widened and the spurs dividing the bronchi of the right middle lobes were thickened. There was much exudate in the left main bronchus, and thickening of the mucous membrane of the left lower branch. The bronchial secretions were watery and no growth was obtained, though the culture of gauze pad containing mucus from the lower left bronchus yielded H. influenza. The sputum showed clumps of pus and a pronounced increase in eosinophiles. The culture revealed Streptococcus viridans, diphtheroids and gram-negative diplococci. The abdomen was soft and nontender and there were no masses. A right indirect inguinal recurrent hernia was present. *The prostate was soft and not enlarged.* The urine showed no albumin or glucose and the microscopic examination was negative. The patient was given penicillin aerosol with negative pressure: a salt free diet and ammonium chloride were prescribed. The nasal secretions diminished, but the asthma persisted.

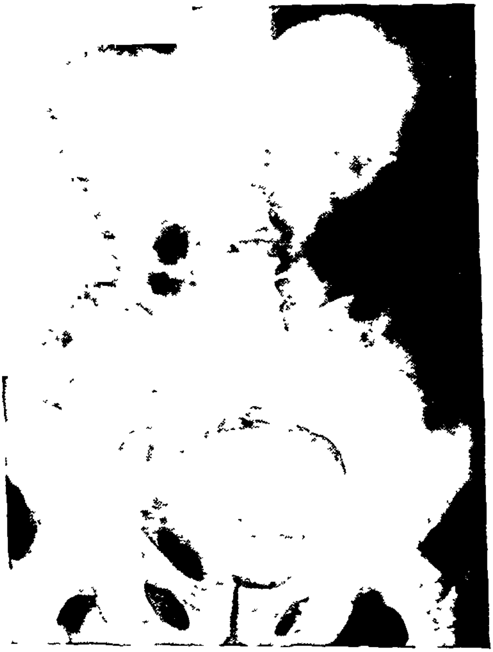

FIG. 1. Excretory urogram. 40 minute film. Note large filling defect in bladder shadow due to prostatic intrusion.

The patient was re-admitted 11 months later (February 1949) because of severe wheezing and cough. He had lost over 50 pounds. He complained of sudden onset of frequency, dysuria and nocturia. Digital palpation of the prostate, rectally, showed it to be *considerably enlarged and firm.* A repeat bronchoscopy revealed much tenaceous thick mucus. There was an eosinophilia of 15 per cent. The urine showed a specific gravity of 1.012, albumin 2 plus, glucose negative, and numerous red and white blood cells. The serum acid phosphatase was 2.1 mg. per cent Bodansky units. The blood pressure was 170/110. Radiographs of the urinary tract (55236) revealed normal renal outlines. Excretory urograms (at 10, 40, and 75 minutes) revealed good excretion and concentration of the dye by both kidneys. The pelves and calyces appeared normal. Both sides emptied well. The bladder outline showed a marked elevation consistent with a *tremendous prostatic enlargement* (fig. 1). A post voiding cystogram showed considerable retention of the dye and a residual of 400 cc was obtained on post voiding catheterization. Cystoscopy showed a markedly trabeculated bladder, and an intrusion by an enlarged prostate. A "rough spot" was seen on the floor, just above the trigone, which did not resemble tumor. On February 21, 1949, Dr. J. Lattimer performed a suprapubic prostatectomy.

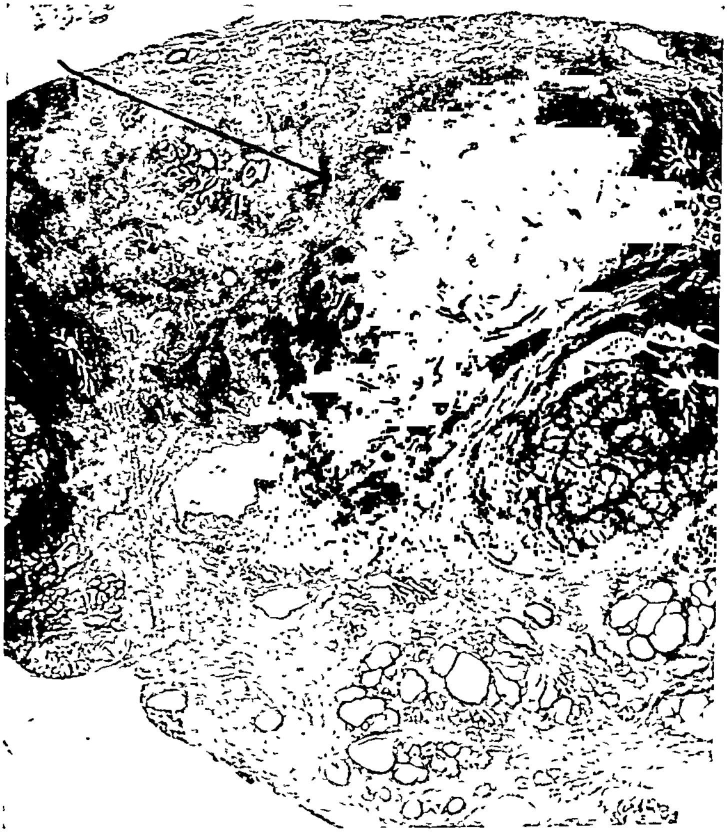

FIG. 2. Topographical view (X 6) of one of lobes of prostate gland. Note multiple granulomas.

Pathology report, GU 8848 (Dr. Melicow): The gross specimen consisted of one lobe of the prostate measuring 3.5 by 2.5 by 2 cm. and two other smaller irregular pieces of prostatic tissue. Their total weight was 14 gm. All were of even, firm consistency and on section, revealed a homogeneous yellow-white surface studded with small firm nodules. There was no gross evidence of malignancy.

Microscopic: In addition to the picture of benign hypertrophy of the prostate gland the sections showed scattered *irregular deeply pink staining areas that were granulomatous in appearance.* (fig. 2). A few giant cells were seen, but other stigmata of tuberculosis were lacking. The high power revealed that the reddish areas were composed of disintegrated connective tissue fibres surrounded by an *intense eosinophilic infiltration* (fig. 3). Some round cells, plasma cells and lymphocytes were also present. Parts of the tortuous wall and lumen of a small blood vessel were seen. The intima was thickened and the media was partially degenerated. A pronounced eosinophilic infiltration was present (fig. 4). Diagnosis: Allergic granulomas of the prostate gland.

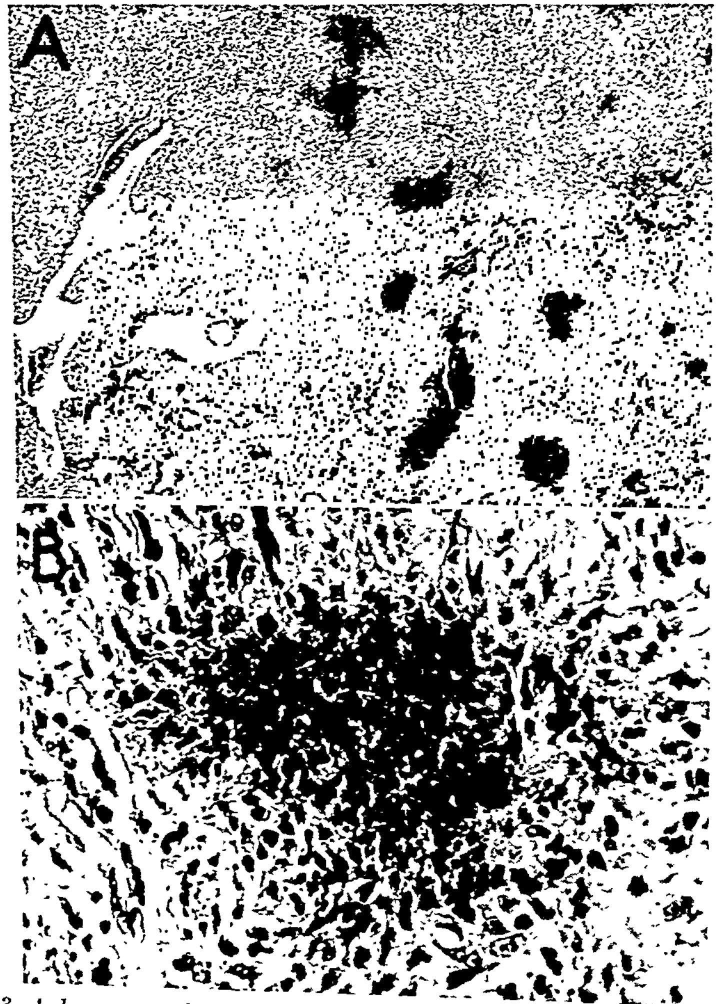

FIG. 3. *A*, low power view (× 50) of multiple granulomas. Several small acini are present nearby. *B*, high power view (× 385) of granuloma. Note central disintegrated connective tissue fibres and abundant cellular exudate which is predominantly of eosinophiles (H and E stain).

The postoperative course was marked by a moderate fever (to 101 F) and hiccough. The patient was discharged on the twenty-third postoperative day, given isuprel, to be used in neublizer, and aminophyllin, for relief of asthmatic attacks.

He returned to the medical ward because of exacerbation of the attacks of asthma. On March 28, 1949, a radiograph of the chest (fig. 5, *A*) revealed a shadow in the left upper lung field at the level of the second rib, which was not seen in the previous film and was suggestive of a localized area of pneumonitis, possibly *tuberculous in origin.* Smears of sputum (Ziehl-Neelsen), were negative for acid-fast organisms. A Petragnnai culture was also negative. Two 24 hour specimens of concentrated sputum were negative for acidfast bacilli. A guinea pig, inoculated with sputum, showed no evidence of tuberculosis at subsequent autopsy. The *eosinophiles rose to 37 per cent.* Another radiograph of the chest (fig. 5, *B*), taken on April 18, 1949, showed a remarkable clearing of the left apical density. This relatively rapid change associated with the history of asthma, eosinophilia and particularly with the pathological finding of allergic granulomas in the prostate gland suggested that the lung lesions were either small infarcts or eosinophilic infiltrations (Loffler syndrome).

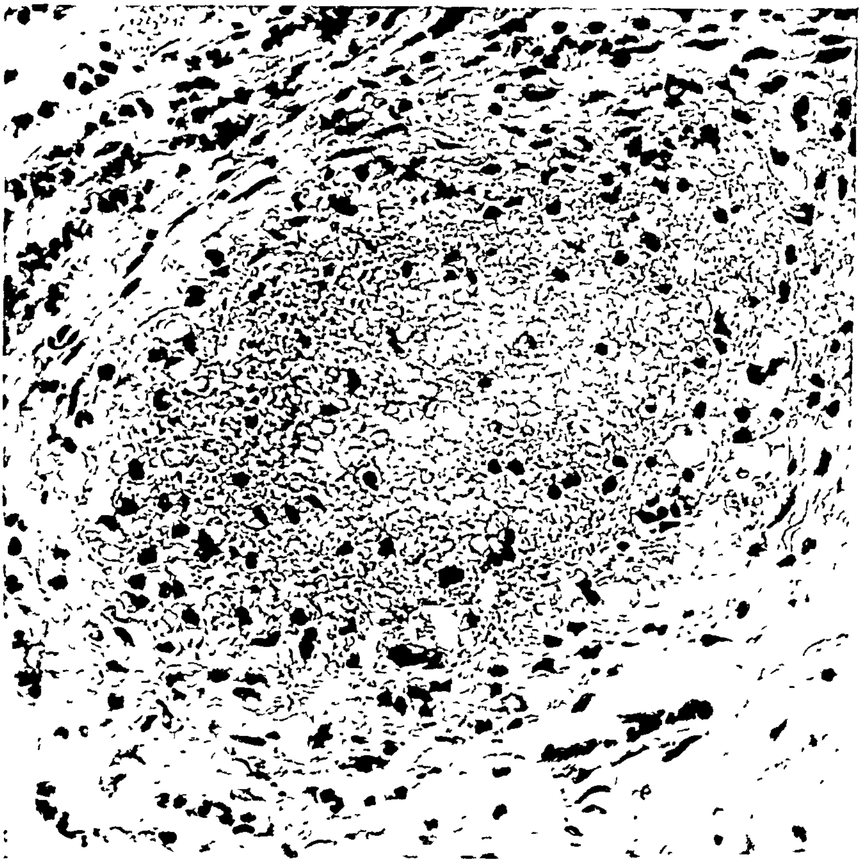

FIG. 4 High power view (X 420) of section of prostatic vein showing intimal proliferation. Perivascular infiltration contained many eosinophiles

Following his discharge from the Presbyterian Hospital, the patient continued to suffer from loss of weight, diarrhea and asthma. On June 2, 1949, he was admitted to the Montefiore Hospital where the large right indirect inguinal hernia which was causing pain was operated on. He was allowed up within 4 weeks. The asthma, in the interim, increased in severity. The blood eosinophiles ranged from 2 to 36 per cent. The patient developed abdominal cramps and diarrhea Barium enemas revealed "inflammatory lesions of the recto-sigmoid". Three sigmoidoscopies with biopsy revealed "inflammation". Bilateral edema appeared in the lower extremities and it was noted that the patient had thrombophlebitis. He received dicumarol but shortly developed hematemesis and melanotic stools. The prothombin time was 24/59 seconds (control 13/25 seconds). He was given whole plasma, blood plasma and 72 mg. vitamin K. The sclerae became icteric. Left lower lobe bronchopneumonia with pleural effusion developed. The temperature rose to 103 F, and there was a marked exacerbation of the asthma. The patient failed to respond to penicillin, sulfa drugs, streptomycin and a thoracentesis. The red blood cell count dropped to 1,640,000 and the hemoglobin to 5.5 gm. The white blood cell count increased to 48,000 with neutrophiles rising to 75 per cent, but for the first time no eosinophiles were found. A 1,500 cc blood transfusion was given. The fever continued, and on September 22, the patient went into coma and died.

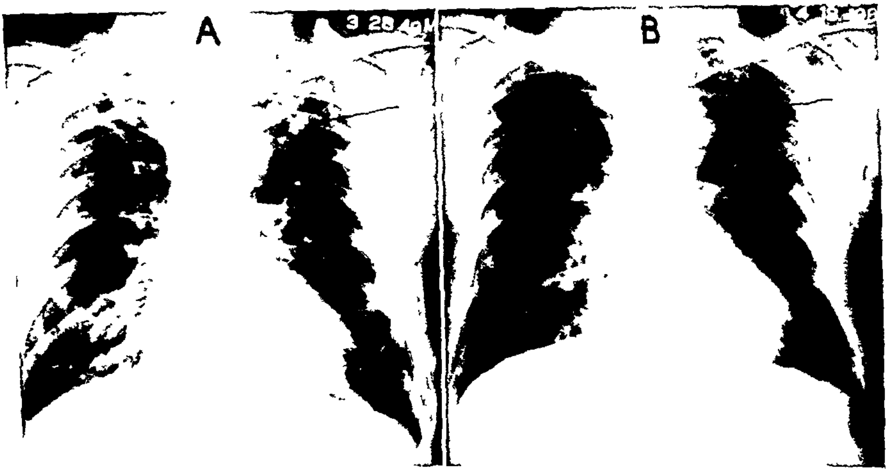

Fig. 5. Radiographs of chest. *A*, note shadow in left upper lung field at level of second rib. Area interpreted as localized pneumonitis of tuberculous origin. *B*, three weeks later. Note resolution of density on left side. This change, plus finding of allergic granulomas in prostate gland, led to diagnosis of eosinophilic infiltrations (Loffler syndrome).

The post-mortem examination was performed by Dr. S. Bernstein at the Montefiore Hospital (No. 11743). In reply to our request for a report of the findings, we received the following summary: "Thickening of the basement membrane of bronchioles; organizing and necrotizing pneumonia of the left lung; *allergic granulomas* in the prostate, bladder, rectum, seminal vesicles, esophagus and heart; healed and healing *periarteritis* in heart and voluntary muscle; disseminated scars in heart, esophagus, bladder, rectum; pericardial adhesions, chronic cystitis and ureteritis; necrotizing esophagitis; interstitial nephritis; hyperplasia of the bone marrow."

DISCUSSION

There are a number of interesting features in this case. The prostate gland was relatively normal on the first admission, and became suddenly enlarged a year later. Numerous areas of a unique type of necrosis (fibrinoid), surrounded by eosinophiles, were present. The clinical course and autopsy findings corroborated the inference that these lesions, i.e., allergic granulomas, were local manifestations of a generalized vascular and connective tissue disturbance. H. Bergstrand[1] showed lesions in lungs and myocardium in patients with "polyarthritis rheumatica, periarteritis nodosa, transient eosinophilic infiltrations of the lung and other allergic syndromes" that were almost identical with those that were found in our patient's prostate (compare figure 6 with figure 4).

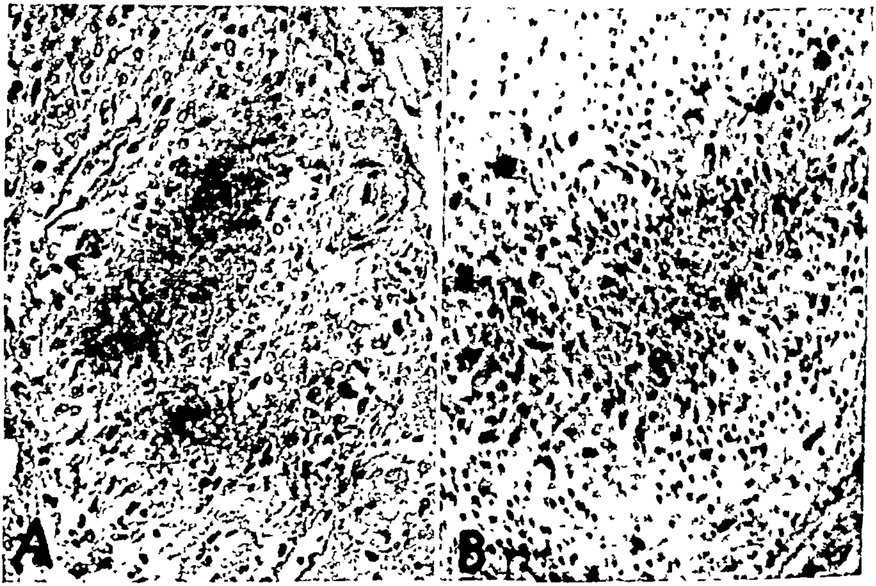

Fig. 6. Black and white reproductions of color prints from article by Bergstrand. Allergic granuloma of *A*, heart and *B*, lung. Note similarity to allergic granulomas of prostate gland.

The sudden involvement, by the granulomas, caused our patient's prostate gland to swell considerably and induce the rapid onset of symptoms of bladder neck obstruction. Several reports of infarcts of the prostate gland have been published; a considerable number of such lesions were seen by us at the Presbyterian Hospital. In many, the infarcts were fresh and, in such instances, they, like the allergic granulomas, could have caused a sudden onset of frequency and nocturia. It is, therefore, important for the urologist to recognize that there may be other factors that can cause prostatic enlargement, besides those which produce the so-called benign hypertrophy (i.e., benign or nodular hyperplasia, or fibroadenomas). It is logical to accept the implication that the prostate enlarged suddenly because of the numerous foci of necrosis which seem to have developed in it in an explosive manner.

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[1] Bergstrand, H.: Morphological equivalents in polyarthritis rheumatica, periarteritis nodosa, transient eosiniphilic infiltration of the lung and other allergic syndromes. J. Path. and Bact . 58: 399, 1946.

The evanescent lung lesions, as demonstrated in successive radiographs of the chest, were probably due to eosinophilic infiltrations, first described by Loffler.[2] He noted that the lesions formed rapidly and disappeared in 3 to 8 days, only to reappear at the same place or elsewhere in the lung. In some patients, the condition persisted for months, and even years. The syndrome occurred in association with hay fever, angioneurotic edema, vasomotor rhinitis, urticaria, pseudo-appendicitic irritation and asthma. Von Meyenburg[3] reported 4 autopsy cases with lung lesions that were characteristic; a pronounced eosinophilic infiltration of the interstitial tissues, giant cells in alveoli, granulomas and small areas of thrombophlebitis. The transient lung infiltrations, furthermore, resemble the lesions of so-called rheumatic pneumonia described by Naish,[4] Gouley and Eiman,[5] and Rich and Gregory.[6] Recurrent pulmonary infiltrations and eosinophilic polyserositis, in patients with vascular allergy and bronchial asthma, were reported by Harkavy.[7]

It is of interest to note that the post-mortem examination of our case revealed granulomatous lesions in the lungs, heart, liver, spleen, eosphagus, rectum and seminal vesicles which were similar to those found in the bladder and prostate following operation. Maier[8] reported instances of eosinophilic infiltrations in the epididymis in patients with the Loffler syndrome.

The bloody diarrhea and abdominal pain were present before the patient received dicumarol and could have been caused by the allergic granulomas of the intestinal tract. The cardiac lesions, too, were of a similar nature. Friedberg and Gross noted "abdominal rheumatism" in patients with periarteritis nodosa associated with rheumatic heart disease.[9] Allen reported a case of periarteritis nodosa with symptoms simulating an acute abdominal condition which came to operation.[10]

The role that the sulfa medication played in the genesis of the allergic syndrome, in our patient, is problematical. We are not sure whether the "asthma" etc., preceded the taking of the drug, or whether it initiated the symptoms. We do know that he could not tolerate the medication, and became worse after taking it. Rich and Gregory[6] showed that patients with hypersensitiveness to sulfa preparations, developed changes in the lungs that resembled those seen in "rheumatic pneumonia". Oelsen and Myschetsky[11] reported a case of periarteritis nodosa presumably caused by sulfonamides.

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[2] Loffler, W.: Respiration und Tuberkulose. Schweiz. Med. Wschr., 66: 1069, 1936.

[3] von Meyenburg, H.: Das eosiniphile Lungeninfiltrat pathologische Anatomie und Pathogenese. Schweiz. Med. Wschr., 72: 809. 1942.

[4] Naish, A. E.: The rheumatic lung. Lancet, 2: 10, 1928.

[5] Gouley, B. A. and Eiman, J.: The pathology of rheumatic pneumonia. Am. J. Med. Sc., 183: 359, 1932.

[6] Rich, A. R. and Gregory, J. E.: On the anaphylactic nature of rheumatic pneumonitis. Bull. Johns Hopkins Hosp., 73: 465, 1943.

[7] Harkavy, J.: Vascular allergy pathogenesis of bronchial asthma with recurrent pulmonary infiltrations and eosinophilic polyserositis. Arch. Int. Med., 67: 709, 1941.

[8] Maier, C.: Das fluchtige eosinophile Lungeninfiltrat zusammenfassende Ergebnisse von uber 100 Beobachtungen. Helvet. Med. Acta, 10: 95, 1943.

[9] Friedberg, C. K. and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, with note on abdominal rheumatism. Arch. Int. Med., 54: 170, 1934.

[10] Allen, P. D.: Periarteritis nodosa simulating an acute abdominal condition requiring operation. Arch. Surg., 40: 271, 1940.

[11] Olesen, H. and Myschetzky, A.: Periarteritis nodosa. A case presumably caused by sulfonamides. Acta. Path. et Microb. Scand., 26: 114, 1949.

SUMMARY

A 62 year old man, who had been suffering from "asthma" for 13 months, was admitted to the Presbyterian Hospital because of severe dyspnea and wheezing. Digital examination of the prostate showed it to be normal in size and consistency. A year later, the patient returned because of the sudden onset of dysuria, frequency and nocturia. Examination revealed a "tremendously enlarged prostate gland," and a suprapubic prostatectomy was performed. Microscopic examination of sections of the prostate gland revealed numerous reddish-staining foci of fibrinoid degeneration, which resembled somewhat the caseation of tuberculosis, but which were free of epithelioid and giant cells. A significant additional finding was the presence, in large number, of eosinophiles surrounding the granulomas. The pathological findings helped to clarify the clinical course, explained the eosinophilia and placed the patient in the category of those suffering from a diffuse vascular allergic dyscrasia. The suspicion of periarteritis nodosa arose, but biopsies of muscle and skin were negative. The lung lesions were interpreted as "eosinophilic infiltrations" (Loffler syndrome). They cleared within three weeks. Several months later the patient's asthma returned, he developed fever, a bloody diarrhea, went steadily downhill and died. The post mortem examination revealed the effects of a diffuse vascular "allergic" syndrome that involved the lungs, heart, eosphagus, rectum, bladder, prostate and seminal vesicles.

It would be of interest, in view of the pronounced eosinophilic reaction, to note the effect that ACTH or cortisone might have on similar cases of allergic granulomas.

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LEIOMYOMA OF THE PROSTATE

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While leiomyoma arising in the uterus constitutes the commonest tumor of the body, its occurrence is rare in other organs. Although minute leiomyomatous nodules are rather common, true leiomyomas of the prostate are rare. It is apparent from the variation in the specimens reported as leiomyoma that there is no strict definition. This is understandable because often the origin of the lesion cannot be proved unequivocally, and secondly, the differentiation of hyperplasia from neoplasm is sometimes impossible even by the experienced pathologist. For the sake of convenience we have arbitrarily defined leiomyoma of the prostate as follows: A circumscribed or encapsulated mass of smooth muscle, 1 cm. or more in diameter, containing varying amounts of fibrous tissue but devoid of glandular elements, and which is either obviously prostatic or juxtaprostatic in origin and position. By this definition we eliminate most cases of fibromuscular hyperplasia, bladder neck tumors and clinically insignificant nodules which create discrepancies in the literature.

Patch and Rhea state that minute leiomyomatous nodules occur commonly in benign hyperplasia of the prostate. In a comprehensive study they made large or whole sections of surgically removed glands and were able to demonstrate nodules varying in size from 0.5 to 3.0 mm. in 25.4 per cent of 181 consecutive cases. They agree, however, that larger smooth muscle tumors of the prostate are rare. Using the definition above, we have found 35 cases previously reported (table 1), and we are adding 3 additional cases.

CASE REPORTS

Case 1. M. R., No. 21387, an 80 year old white man of Russian descent, was admitted to the ward urological service of the New Haven Hospital on September 2, 1939. He complained of gradually increasing frequency and hesitancy, culminating in complete retention 5 days prior to admission. He had been catheterized twice daily since that time. There were no other significant facts in the past history and the family history was noncontributory.

Physical examination revealed a well developed man whose temperature was 99.6F and whose blood pressure was 145/70. He had large bilateral inguinal hernias. On rectal examination the prostate was found to be 3 or 4 times normal size and elastic in consistency.

Urinalysis revealed albumin 1 plus, 3–5 white blood cells, 1–2 red blood cells per high power field and staphylococci and B. coli on stained smear and culture. The serological test for syphilis was negative. The nonprotein nitrogen was 29. On the phenolsulfonphthalein test there was 60 per cent excretion in 1 hour and

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etc., preceded the taking of the drug, or whether it initiated the symptoms. We do know that he could not tolerate the medication, and became worse after taking it. Rich and Gregory[6] showed that patients with hypersensitiveness to sulfa preparations, developed changes in the lungs that resembled those seen in "rheumatic pneumonia". Oelsen and Myschetsky[11] reported a case of periarteritis nodosa presumably caused by sulfonamides.

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Neupert	1931	67	Urinary	Laparotomy	Retroperitoneal mass arising from prostatic area	3600 gm.	Fibromyoma of the prostate (no glandular elements)	Died 21 hours.
Deuticke	1932	65	Rectal	Perineal	Intraprostatic globular masses	Estim 10 cm. diam.	Composed of smooth muscle with no epithelial elements.	Recovery
Dial and Halpert	1933	59	Urinary	Suprapubic	Intraprostatic	2 cm. diam.	Composed of smooth muscle with no epithelial elements. Other parts of prostate, glandular hyperplasia.	Recovery
		65	Urinary, complete retention	Perineal	Intraprostatic	1 2 cm. diam.	Typical smooth muscle tumor devoid of glandular elements.	Recovery
		67	Urinary	Suprapubic	Intraprostatic; median lobe	2 cm. diam.	Typical circumscribed smooth muscle tumor devoid of glandular elements.	Recovery
Mitchell & Blaisdell	1933	62	Urinary, complete retention	Suprapubic	Intraprostatic	4.5 cm. diam. 35 gm.	Composed of smooth muscle fibers devoid of glandular elements.	Recovery
Powell	1933	76	Urinary	Suprapubic	Intraprostatic	Estimated 2 x 1.5 x 1 cm.	Encapsulated smooth muscle tumor with adenomatous hyperplasia in other parts of the prostate.	Recovery
Patch and Rhea	1935	80	Urinary, complete retention	None. Autopsy	Intraprostatic projecting into bladder	13.5 cm. diam.	Encapsulated smooth muscle tumor without glandular elements.	Dead
Kornitzer	1935	53	Urinary	Suprapubic	Projecting at bladder neck	Estimated 2 cm. diam.	Pure leiomyoma, circumscribed, with scattered round cell foci.	Recovery

AUTHOR	DATE	AGE	SYMPTOMS	OPERATION	POSITION	SIZE	PATHOLOGIC DESCRIPTION	RESULT
Lebec	1876	76	Urinary	None. Autopsy	Middle lobe	3 cm. diam.	Encapsulated tumor of smooth muscle fibers similar to smooth muscle tumor of uterus.	Died; pneumonia
Vignolo	1922	63	Rectal	Perineal	Posterior (perineal)	250 gm.	Fibromyoma with no trace of glandular elements	Recovery
Tandler & Zuckerkandl	1922	65	Urinary, Complete retention	Suprapubic	Lat. lobe	100 gm.	One lobe smooth muscle hyperplasia without glands; one lobe glandular hyperplasia.	Recovery
Damski	1921	62	Rectal	Perineal	Posterior (perineal)	180 gm.	Composed entirely of interlacing smooth muscle fibers	Recovery
Bugbee	1926	19	Urinary, Complete retention	Perineal	Intraprostatic	360 gm.	Composed entirely of smooth muscle cells. Infrequent mitoses. ? malignant	Recovery X-ray treatment
Rubritius	1927	70	Urinary	Suprapubic	Mass protruding into bladder	Estimated 7 cm. diam.	Encapsulated smooth muscle tumor without glandular elements.	Recovery
Wolman	1931	73	Urinary, Complete retention	None. Autopsy	Ant. to urethra	1.9 x 1.8 x 1.2 cm.	Encapsulated smooth muscle tumor with scanty conn. tiss. stroma and no glandular elements	Died Pneumonia
Hinman & Sullivan	1931	36	Rectal	Perineal	Posterior pedunculated	2.5 x 3.5 x 4.5 cm.	Discrete tumor of interlacing strands of smooth muscle with no glandular elements	Recovery
		39	Rectal	Perineal & autopsy	Posterior	3 x 2 x 2 cm. 5	Discrete tumor of irregular bundles of smooth muscle cells with	Died 21 hours.

Neupert	1931	67	Urinary	Laparotomy	Retroperitoneal mass arising from prostatic area	3600 gm	Fibromyoma of the prostate (no glandular elements)	Died 21 hours.
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		65	Urinary, complete retention	Perineal	Intraprostatic	1.2 cm diam	Typical smooth muscle tumor devoid of glandular elements	Recovery
		67	Urinary	Suprapubic	Intraprostatic, median lobe	2 cm diam.	Typical circumscribed smooth muscle tumor devoid of glandular elements.	Recovery
Mitchell & Blaisdell	1933	62	Urinary, complete retention	Suprapubic	Intraprostatic	1.5 cm. diam 35 gm	Composed of smooth muscle fibers devoid of glandular elements.	Recovery
Powell	1933	76	Urinary	Suprapubic	Intraprostatic	Estimated 2 x 1.5 x 1 cm	Encapsulated smooth muscle tumor with adenomatous hyperplasia in other parts of the prostate.	Recovery
Patch and Rhea	1935	80	Urinary, complete retention	None. Autopsy	Intraprostatic projecting into bladder	13.5 cm diam	Encapsulated smooth muscle tumor without glandular elements.	Dead
Kornitzer	1935	53	Urinary	Suprapubic	Projecting at bladder neck	Estimated 2 cm. diam	Pure leiomyoma, circumscribed, with scattered round cell foci.	Recovery

Table 1—*Continued*

AUTHOR	DATE	AGE	SYMPTOMS	OPERATION	POSITION	SIZE	PATHOLOGIC DESCRIPTION	RESULT
Kornitzer—*Continued*		73	Urinary, complete retention	Suprapubic	Projecting at bladder neck.	Estimated 5 cm. diam.	Pure circumscribed smooth muscle tumor	Recovery
Akin	1936	48	Urinary, priapism	TUR	Pedunculated extending into urethra		Smooth muscle tumor with no glandular elements. Lymphocytic infiltration.	Recovery
Baretz	1936	76	Urinary, complete retention	Suprapubic	Intraprostatic	Estimated 2 x 1 x 1 cm.	Circumscribed and encapsulated areas of interlacing bundles of smooth muscle. Other areas show glandular hyperplasia and prostatitis.	Recovery
Pratt	1936	73	Urinary, complete retention	Suprapubic	Intraprostatic. Lat. lobes	3.5 x 5 cm.	Two distinct leiomyomata. Encapsulated smooth muscle tumors without glandular elements.	Recovery
Koenig	1936	21	Rectal	Perineal biopsy Suprapubic	Rt. posterior	181 gm. 12 x 8 x 6 cm.	Encapsulated smooth muscle tumor without glandular elements. Delicate conn. tiss. stroma.	Recovery
Mimpriss	1936	60	Urinary, complete retention	Suprapubic	Intraprostatic.	570 gm.	Circumscribed smooth muscle tumor with no epithelial elements.	Died 20 hours
Heggie	1936	69	Urinary, complete retention	Suprapubic	Intraprostatic middle lobe	1.5 cm. diam.	Circumscribed fibromyoma	Recovery

		33	Urinary	Suprapubic	Intraprostatic.	95 gm.	Fibromuscular hypertrophy with no glandular elements and with small areas (2–5 mm.) of pure smooth muscle masses.	Died Pneumonia Hemorrhage
		71	Urinary, complete retention	Suprapubic	Middle lobe intraprostatic	98 gm.	Circumscribed, almost pure leiomyoma with no glandular elements.	Recovery
Wyler	1939	37	Urinary	Perineal	Intraprostatic	7 x 4.5 cm.	Sharply demarcated tumor of smooth muscle fibers with no epithelial elements.	Recovery
Keen	1939	62	Urinary, complete retention	Suprapubic	Intraprostatic	4.5 x 3 cm.	Circumscribed tumor of interlacing bundles of smooth muscle with no glandular tissue.	Recovery
Magoun	1939	60	Urinary & rectal	None. Autopsy	Mass arising from base of bladder, replacing prostate.	1450 gm.	Smooth muscle tumor devoid of epithelial elements.	Dead
Neuswanger	1939	73	Urinary	Suprapubic	Intraprostatic	3 x 5 cm.	Smooth muscle tumor circumscribed and without glandular elements.	Recovery
Pelkonen	1946	69	Rectal	Suprapubic	Lat. lobes, pointing posteriorly	350 gm.	Circumscribed tumor of interlacing smooth muscle bundles without acini.	Recovery
McIntyre	1948	71	Urinary & rectal	Suprapubic cystotomy & TUR	Intraprostatic, pointing anteriorly.		Nodular mass composed of smooth muscle fibers with no glandular elements.	Recovery

Table 1—*Continued*

AUTHOR	DATE	AGE	SYMPTOMS	OPERATION	POSITION	SIZE	PATHOLOGIC DESCRIPTION	RESULT
Carson	1950	65	Urinary, complete retention	Perineal	Intraprostatic arising from region of veru montanum	112 gm. 7.2 x 5.5 x 3.9 cm.	Pure leiomyoma with foci of hyalinization	Recovery
Gray & Thompson	1950	59	Urinary	TUR	Middle lobe intravesical enlargement	148 gm.	Degenerating leiomyoma with degeneration giant cells.	Recovery

20 per cent during the second hour. An x-ray of the chest showed slight enlargement of the left ventricle with widening, lengthening and caclification of the aorta.

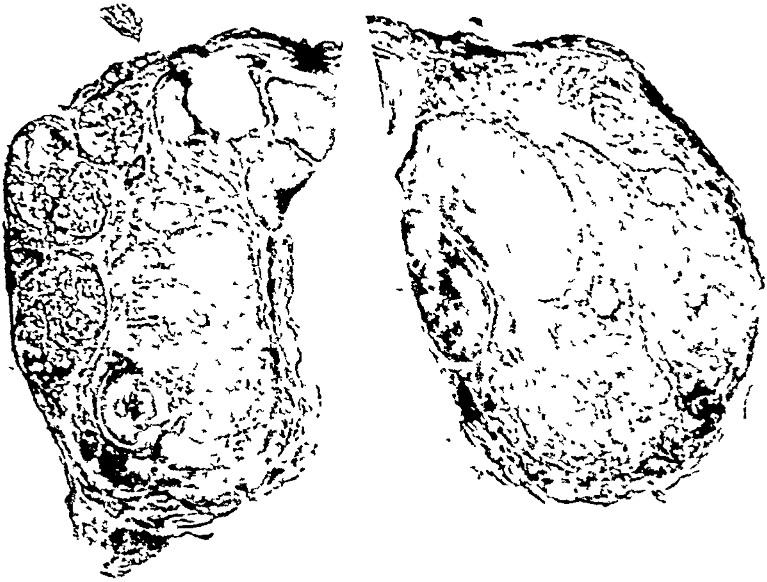

FIG 1 Whole section of prostate × 2 Leiomyoma has displaced hyperplastic glandular tissue to periphery

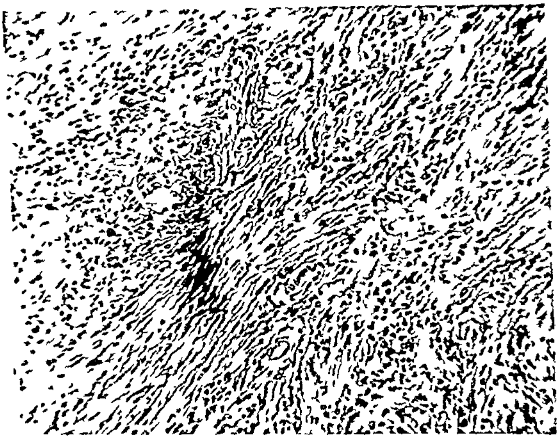

FIG 2 Photomicrograph of leiomyoma × 200. Note interlacing smooth muscle fibers and sparse lymphocytic infiltration

Cystoscopy revealed a bladder capacity of 300 cc. The bladder wall was trabeculated and inflamed, but otherwise normal. There was intra-urethral intrusion of both enlarged lateral prostatic lobes.

On September 15, 1939, under general anesthesia, perineal prostatectomy was performed. The specimen weighed 85 gm. On cut section the specimen presented a whorled appearance with a watered-silk luster. On microscopic examination the tissue was found to consist chiefly of dense fibromuscular stroma, the major portion of which was devoid of glandular elements. The tissue was cellular and arranged in whorls. There was a diffuse sparse infiltration by lymphocytes. The few glandular elements of the specimen were displaced to the periphery by the leiomyoma and consisted of nests of acini lined by tall columnar epithelium. There were some areas of cystic dilatation seen and in these the epithelium was flattened (figs. 1 and 2). The pathologic diagnosis was leiomyoma of the prostate associated with benign hyperplasia. The patient had an uneventful postoperative course.

Case 2. W. L., No. 46379, was a 63 year old white man who entered the Veterans Administration Hospital, Newington, Conn. on October 18, 1948, for re-evaluation of skin tumors of the face. The patient had been admitted on 4 previous occasions. Diagnoses on these entries included hydrocele, varicocele, hemorrhoids, inguinal hernias and basal cell tumors of the face. His last admission was 5 months previously at which time rectal examination was allegedly negative. On his present admission rectal examination revealed a rubbery, firm mass about 2 by 2 cm. in size at the apex of the prostate. This was nontender, had a fixed base and did not invade the rectal mucosa. It was clearly defined and seemed pedunculated. On review of the patient's history, he stated that for about 6 months prior to the present admission he had had mild rectal tenesmus. There was no history of constipation, melena, diarrhea or other changes in the bowel habits. He denied urinary symptoms.

Urinalysis revealed a specific gravity of 1.025, albumin 1 plus, and a normal microscopic examination. Urine smear and culture were negative. The nonprotein nitrogen was 29 mg. per cent. The blood count was normal. Acid phosphatase was 2.5 King-Armstrong units and alkaline phosphatase was 7.45 King-Armstrong units.

Cystoscopy revealed no bladder residual and a bladder capacity of 400 cc. The bladder wall and trigone appeared normal. On the surface of the verumontanum there was an irregular opening representing a patulous orifice of the sinus pocularis. The position of the nodule at the apex of the prostate was confirmed by recto-urethral palpation with the cystoscope in place. The differential diagnoses were müllerian duct cyst, carcinoma of the prostate and adenoma. On November 10, 1948, under spinal anesthesia, perineal exposure of the prostate was done. A well encapsulated ovoid mass, 2 by 3 cm. in size, was found at the apex of the prostate. This was enucleated with ease and a frozen section was reported as leiomyoma. The remainder of the prostate was left in situ. Postoperative course was uneventful. Pathological report of the tumor removed was as follows: "Specimen consists of a rubbery yellow-pink ovoid piece of tissue 2.5 by 2 by 1.5 cm. in size. Cross section reveals glistening homogenous gray-yellow cut surface with whorled appearance. Microscopic examination reveals interlacing whorls of smooth muscle cells with rich acidophilic cytoplasm and long cylindrical sausage-shaped vesicular nuclei with rounded ends. There is no evidence of glandular elements, nor is there evidence of cellular anaplasia. Diagnosis: Leiomyoma of the prostate."

While the patient was in the hospital, multiple basal cell tumors of the face were removed. This patient has been followed for 6 months following the myomectomy. His preoperative rectal complaints were allayed by the operation and rectal examinations during the postoperative period to date have revealed a prostate of normal contour, consistency and size.

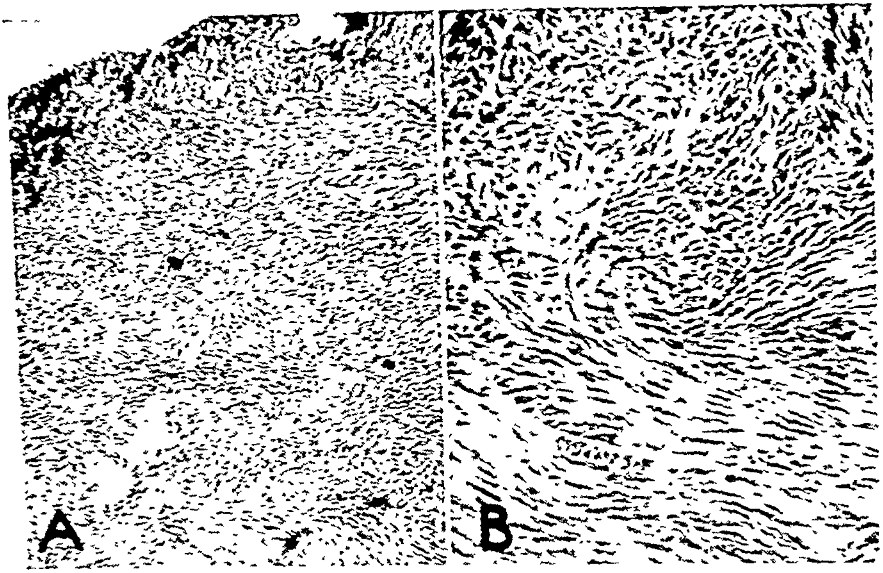

FIG. 3. Case 2. *A*, photomicrograph of leiomyoma × 100. Tumor consists of smooth muscle bundles and is devoid of glandular elements. *B*, × 500. Note whorls of smooth muscle fibers.

Case 3. W. B., No. 51,543, a 62 year old white man, entered the Veterans Administration Hospital, Newington, Conn. on October 31, 1949 complaining of abdominal pain and weight loss of 5 months' duration. The symptoms began insidiously with right lower quadrant pain radiating to the left lower quadrant, occurring once or twice a week and lasting 30 minutes. This symptom was superseded by episodes of right upper quadrant pain radiating across the upper abdomen, occurring 30 minutes after meals and accompanied by transient nausea. The patient had lost 20 pounds in the preceding 5 months. He also stated that he had been subject to chronic constipation for the past 10 years, but that there had been no change in the character of the stools. He denied melena and dyschezia. During the 4 months prior to his admission he had noted nocturia 1 to 3 times, slight hesitancy and slight reduction in the force of the urinary stream.

Physical examination revealed a liver edge palpable three fingerbreadths below the right costal margin, a reducible left inguinal hernia, and an unusual prostate. The latter was described as being twice normal size, with a firm, discrete pedunculated, cherry-sized nodule on the left lobe.

Laboratory data included normal hematological findings, clear urine which contained no albumin or significant sediment on repeated examinations, normal liver function tests, negative stool examinations, and a serum acid phosphatase value of 2.7 King-Armstrong units. Additional diagnostic studies included electrocardiograms, a gallbladder series, metastatic series, and sigmoidoscopy, all of which were indeterminate. A barium enema revealed slight narrowing in the mid transverse colon.

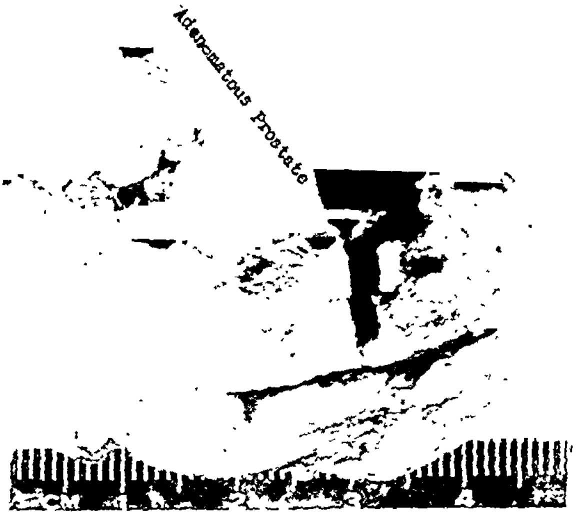

FIG. 4. Case 3. Surgical specimen showing pedunculated leiomyoma

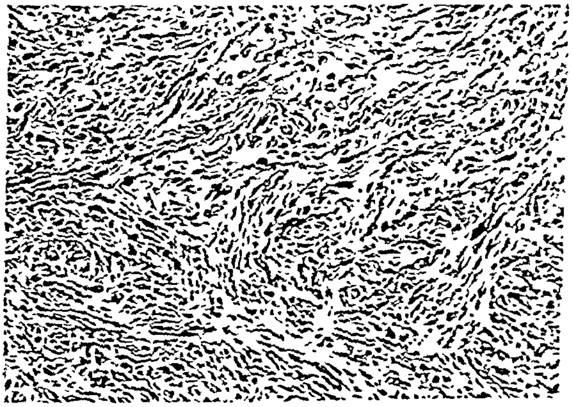

FIG. 5. High power photomicrograph showing interlacing smooth muscle bundles and absence of glandular elements.

Prior to re-examination of the bowel, urological evaluation was deemed advisable because several observers agreed that the prostatic nodule deserved investigation to rule out carcinoma. On November 7, 1949, cystoscopy disclosed residual urine 15 cc; the bladder capacity was 200 cc. There was moderate trabeculation and cellule formation, and the lateral lobes of the prostate met in the midline. Recto-urethral palpation of the prostate confirmed the presence of a firm nodule, approximately 2 cm. in diameter, arising posteriorly from the left lobe. The bladder urine showed 10 white blood cells per high power field and no bacteriuria.

On December 2, under spinal anesthesia, perineal exposure of the prostate revealed a pedunculated nodule on the left lobe which was biopsied, and which, on frozen section, proved to contain no carcinoma. Enucleation of the prostate was then carried out. Description of the gross specimen was as follows: "The specimen consists of a prostate which is of pink-gray color, firm consistency and nodular outline, and measures 6 by 3 by 3 cm. Attached to the main portion of the specimen is a pedunculated nodule of firm consistency which measures 2 by 1.5 by 1.5 cm. On cut section, the surface of the main portion of the prostate shows islands of grayish-tan glandular tissue, measuring an average of one cm. in diameter, and surrounded by white fibromuscular stroma. The pedunculated nodule presents a uniform appearance and the cut surface is of glistening, homogeneous character and white color." The microscopic appearance of the leiomyoma was similar to that described in the first two cases, showing interlacing bundles of smooth muscle in a collagenous stroma, frequent whorl formations, and no acinar elements. The main portion of the prostate showed hyperplastic acini regularly disposed throughout the fibromuscular matrix. The leiomyoma was sharply demarcated from the adenomatous prostate and was surrounded by a collagenous capsule.

The patient had an uneventful course, and at discharge, on the seventeenth postoperative day, he was voiding without difficulty and had no evidence of urinary tract infection. He was to return to the hospital after a brief period of convalescence for further evaluation of the gastro-intestinal tract.

DISCUSSION

In the 35 cases heretofore reported, the ages of the patients ranged from 24 to 80 years with an average of 61.4 years. Symptomatology was urinary in 26 cases, rectal in 7 and both rectal and urinary in 2. The average age of patients presenting urinary complaints was 64, the average age of patients with rectal complaints was 54. In most patients with urinary symptoms, the complaints were indistinguishable from those of prostatism. Complete urinary retention occurred in 40 per cent of the cases. The rectal symptoms usually consisted of progressive constipation, obstipation or tenesmus. Of the previously reported cases, 18 were treated by suprapubic prostatectomy, 9 by perineal resection, 3 by transurethral resection and 5 were found at autopsy. Description of the size of the tumors is difficult to summarize because of variation in methods of estimation and because of the lack of exact information in some reports. The largest reported case is that of Neupert in which the specimen weighed 3.6 kg. Of the 13 cases in which specimens were described by weight (aside from the 2 massive tumors described by Neupert and Magoun in which the growths weighed 3.6 kg. and 1.45 kg. respectively) the average weight was 191 gm. Measurements were recorded in only 22 cases and the average was 4.8 by 4.1 by 3.8 cm. In all cases the diagnosis of leiomyoma was confirmed by the microscopic picture of a circumscribed smooth muscle tumor with or without glandular elements in other parts of the specimen. Lateral, median, posterior and combinations of lobes have been involved. It has been shown that the tumors may be either intra- or extraprostatic. In the former group they usually displace the normal or hyperplastic glandular tissue to the periphery and in the latter group they are often pedunculated and produce pressure on neighboring organs such as the rectum. The intraprostatic leiomyomas with intravesical or intra-urethral extension are usually clinically indistinguishable from symptomatic benign prostatic hyperplasia.

There are numerous theories regarding the pathogenesis of leiomyomas of the prostate. Tandler and Zuckerkandl expressed the belief that infection and inflammation transform adenomatous masses of the prostate into smooth muscle with the formation of myomas. Ewing also believed that in chronic prostatitis there may be "hyperplasia" of smooth muscle tissue which at times simulates neoplasm. He also stated, however, that isolated or pedunculated myomas arise in the prostate and that the histology of these is different from that of the "hyperplastic" fibromuscular tissue seen in ordinary hypertrophy and in chronic inflammation. Adrion believed that arteriosclerosis or infection may produce dedgenration of hyperplastic tubular nodules so that only scar tissue and smooth muscle stroma remain. Blum and Rubritius believed that leiomyomas represent fibromuscular "hypertrophy" in an organ in which there is glandular, muscular, and connective tissue and in which any one may predominate in the picture of hyperplasia of the prostate, although the adenomatous hyperplasia is by far the most common. Jacoby contended that pure leiomyomas never occur and that in all cases epithelial elements are found. Patch and Rhea, on the other hand, think that leiomyomas represent bona fide tumors and that they originate from embryological anlagen. They state that true leiomyomas are to be differentiated from the small fibromuscular nodules which are seen frequently in "leiomyomatous forms of prostatic enlargement." Deming believes that prostatic hypertrophy begins as a fibromuscular nodule in the prostatic urethra and that this nodule is invaded by ductal epithelium which in turn may become adenomatous and replace the fibromuscular tissue. He also believes that when there are no adjacent suburethral ducts to invade the primary tumor, the nodule may develop into a large myomatous mass without glandular elements. He supports this contention with the statement that often numerous smooth muscle tumors can be demonstrated in the muscular wall of the posterior urethra. He concurs with Patch and Rhea in their belief that these tumors actually arise from embryologic anlagen. Although Ewing states that an analogy between the etiology of uterine and prostatic myomas cannot be drawn because the two organs are not homologues, Lowsley points out that the lower müllerian duct fibers which form the veru pierce the posterior urethra where they are mixed with the musculature of the urethral wall. Deming believes that the leiomyomas arise from these anlagen situated in the posterior urethra. (Hinman's first case, Carson's case and the authors' second case showed midline tumors posteriorly opposite the verumontanum and support the theory that such growth originated from midline structures, most probably müllerian duct anlagen).

While it is true that leiomyoma of the prostate occurs infrequently enough to consider it a curiosity, it still should be included in the differential diagnosis of prostatic and bladder neck tumors. The preoperative diagnosis can rarely be made in cases where the tumor is intraprostatic and produces bladder neck obstruction unless it is discovered on transurethral biopsy. The disease occurs in the age group in which glandular hyperplasia of the prostate is most common and frequently may be masked by concomitant adenomatous enlargement. Where the tumor is mainly extraprostatic and points posteriorly (as in our case 2 and in 7 other reported cases) it may be confused with carcinoma of the prostate, müllerian duct cyst, prostatic adenoma or prostatic cyst. It should be suspected in cases where there is an extramural anterior rectal mass of elastic or firm consistency.

Where the tumors are intraprostatic, they will be amenable to the standard methods of prostatectomy. If they are extraprostatic they usually can be enucleated with ease. Extirpation of the tumors will result in cure unless sarcomatous change has occurred. No case of recurrence following prostatectomy or myomectomy has been reported. Morbidity and survival following surgery are comparable to those associated with other benign prostatic growths.

CONCLUSIONS

Thirty-eight cases of true leiomyoma of the prostate, including the 3 cases presented in this paper, have been reported.

True leiomyomas of the prostate must be differentiated from the small fibromuscular nodules which are frequently associated with hyperplasia of the prostate.

Leiomyomas of the prostate may be extra- or intraprostatic and may produce either rectal or urinary symptoms.

Various theories as to the pathogenesis of this entity have been presented.

Leiomyoma of the prostate should be suspected when a firm or elastic mass is felt anteriorly on rectal examination.

Prostatectomy or myomectomy (depending on the position of the tumor) usually results in cure.

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REFERENCES

Adrion: Ziegler's Beit. z. path. Anat., 179, 1922.
Akin, R. H.: Urol. & Cut. Rev. **40**: 558, 1936.
Baretz, L. H.: J. Urol., **35**: 664, 1936.
Blum, and Rubritius, H.: Handbuch der Urologie. Berlin: Julius Springer, 1928. vol. 5, p. 508–510.
Bugbee, H. G.: J. Urol., **16**: 67, 1926.
Carson, R. B.: J. Urol., **64**: 373, 1950.
Damski: Ztschr. f. urol. Chir., **16**: 47, 1924.
Deming, C. L.: Trans. Am. Assoc. Genito-Urin. Surg., pp. 263–273, 1939.
Deming, C. L. and Wolf, J. S.: J. Urol., **42**: 556, 1939.
Deuticke, P.: Deutsche Ztschr. f. Chir., **236**: 475, 1932.
Dial, D. L. and Halpert, B.: Arch. Path., **16**: 332, 1933.
Ewing, J.: Neoplastic Diseases. Philadelphia: W. B. Saunders Co., 1940, pp. 239, 842, 4th ed.
Gray, C. P. and Thompson, G. J.: J. Urol., **64**: 511, 1950.
Heggie, J. F.: Glasgow Med. J., **126**: 223, 1936.

Hinman, F. and Sullivan, J. J.: J. Urol., **26**: 475, 1931.
Jacoby, M.: Ztschr. f. urol. Chir., **14**: 15, 1924. Quoted by Patch and Rhea, loc. cit.
Keen, M. R.: J. Urol., **42**: 158, 1939.
Koenig, G. H.: Urol. & Cut. Rev., **40**: 545, 1936.
Kornitzer, E. and Zanger, C.: Ztschr. f. urol. Chir., **11**: 137, 1923.
Kornitzer, E.: Ztschr. f. urol. Chir., **40**: 367, 1934-35.
Lebec: Progres méd., **4**: 471, 1876.
Lowsley, O. S.: Am. J. Anat., **13**: 299, 1912.
Magoun, J. A.: Am. J. Surg., **44**: 474, 1939.
McIntyre, D. W.: J. Urol., **59**: 1198, 1948.
Mimpriss, T. W.: Brit. J. Surg., **23**: 863, 1936.
Mitchell, D. R. and Blaisdell, J. L.: Brit. J. Urol., **5**: 381, 1933.
Neupert: Zentralbl. f. Chir., **58**: 1071, 1931.
Neuswanger, C. H.: Quoted by Deming, Trans. Am. Assoc. Genito-Urinary Surg. pp. 263–273, 1939.
Patch, F. S. and Rhea, L. J.: Brit. J. Urol., **7**: 213–228, 1935.
Pelknonen, A.: Acta Chir. Scandinav. **93**: 352, 1946.
Powell, R. E.: Brit. J. Urol., **5**: 143, 1933.
Pratt, J. G.: New Orleans Med. and Surg. J., **88**: 763, 1936.
Rohrbach, P.: Schweiz. Ztschr. f. Path. u. Bakt., **8**: 145, 1945.
Rubritius, H.: Ztschr. f. urol. Chir., **24**: 418, 1928.
Tandler, J. and Zuckerkandl, O.: Studien zur Anatomie und Klinik der Prostata Hypertrophie. Berlin: Julius Springer, 1922.
Veseen, L. L.: J. Urol., **22**: 302, 1929.
Vignolo: Quoted by Deuticke, P.: loc. cit.
Wolman, I. J.: J. Urol., **25**: 93, 1931.
Wyler, J.: Schweiz. Med. Wchnschr. nr., **15**: 339, 1939.

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THE HEATING EFFECTS OF SHORT WAVE DIATHERMY ON THE PROSTATE OF THE DOG

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It was not until the application of high frequency currents (diathermy) to medicine that satisfactory methods became available for heating the prostate gland. The purpose* of this study was to determine the rises in temperature produced in the prostate gland when exposed to short wave diathermy.

To heat the dog's prostate gland using an external applicator is not satisfactory because the gland normally lies behind the anterior border of the os pubis. This makes it necessary to heat the gland with an internal applicator introduced into the rectum (Hibbs and Osborne). The beneficial effects obtained in treating pathologic conditions of the prostate by heating are attributed to an increased blood flow. Opinions differ regarding the optimal therapeutic temperature. Some workers state that a rise of temperature of 2 F suffices, whereas others consider a rise of at least 5 to 6 F essential.

APPARATUS USED

The high frequency electrical energy described in physical medicine as "short wave diathermy" is generated by a vacuum tube oscillator at a frequency of 10 to 100 megacycles per second with a wavelength ranging from 3 to 30 meters. Short wave diathermy for this study was produced by the De Forest model "NE" dynatherm. This machine has a frequency of 16,600,000 cycles per second with a wavelength of approximately 18 meters. The internal applicator and the applicator pad were of the same type employed clinically.

TEMPERATURE RECORDING

All temperatures were recorded with the bead type thermistor (V642). A thermistor is a thermally sensitive resistor having a large negative temperature coefficient. The electrical resistance variations are recorded by using the thermistor as one arm of a Wheatstone bridge.

The thermistors were so small that they could be easily implanted into various portions of the prostate without causing undue trauma. The wires connecting the thermistors to the bridge circuit absorb energy in an electromagnetic field and so the thermistors could not be used for continuous temperature recordings. Therefore, in these experiments it was necessary to turn off the current at intervals of 5 minutes and allow 15 seconds before recording the temperatures.

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* See addendum.

EXPERIMENTAL PROCEDURE

Dogs were anesthetized by intravenously administered pentobarbital sodium (25 mg. per kilogram of body weight) and the prostate was exposed through a low pararectus incision. Two thermistors were inserted into the prostate, one into the superior aspect of one lobe and the other into the inferior aspect of the opposite lobe. The thermistors were inserted into the lobes of the prostate through hypodermic needles which were withdrawn leaving the thermistors at a depth of about 0.4 cm. In addition, a third thermistor was inserted into the prostatic urethra, and a fourth into the bladder. Then the short wave diathermy applicator, with a thermistor attached over the point of maximal energy emission, was introduced into the rectum and placed in such a position that the midpoint of the superior surface of the prostate rested exactly over the thermistor. The thermistor leads were then brought out through the incision and the abdomen was closed. Finally the applicator pad was placed, between two layers of toweling, on the abdomen just anterior to the scrotum and a series of control temperatures were recorded before exposure to short wave diathermy.

EXPERIMENTAL STUDIES

A series of experiments was performed to determine the heating effects of short wave diathermy on the prostate and to determine the relationship between the prostatic temperature and the rise in rectal temperature.

Dogs were given short wave diathermy for periods of 1 hour and the rectal, prostatic and bladder temperatures were recorded at intervals of 5 minutes.

In these experiments, starting with plate currents of 70 to 75 milliamperes, there was a rapid initial rise in rectal temperature of from 5 to 8F which reached its peak within five to ten minutes. This was followed by a fall in temperature which reached its lowest level five to ten minutes after the initial rise and remained constant within 0.5F for a further period of 20 to 30 minutes, after which a second rise was frequently observed. At the termination of the experiment the rectal temperature fell from 2 to 4F in the first 5 minutes and subsequently returned to the control level in about 15 to 20 minutes.

The fluctuation in prostatic temperature varied directly with the rectal temperature; that was especially evident during the initial rise. The difference in temperature between the rectum and the prostate varied between 0.5 and 2.5F. The portion of the prostate proximal to the rectum was 0.5 to 2F higher than the distal portion.

The temperatures recorded in the prostatic urethra were variable and no definite relationship could be established between them and those recorded in the prostate.

The temperature in the bladder gradually rose and reached a maximal rise of 2F after 20 to 30 minutes of heating. This rise in temperature was not influenced by either the presence or absence of urine in the bladder.

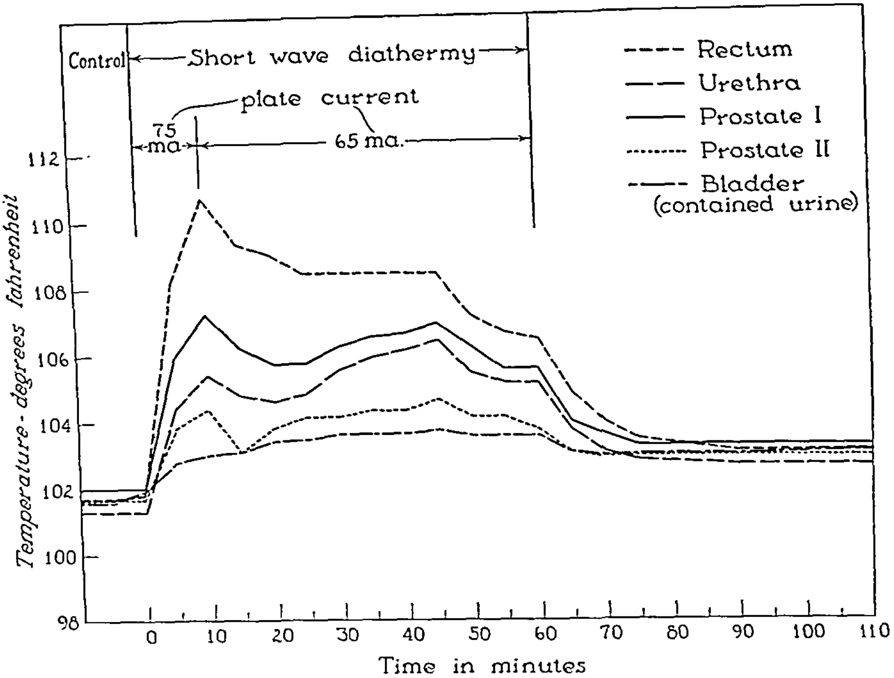

FIG. 1. Rectal, urethral, prostatic and vesical temperatures before, during and after 1 hour of exposure to short wave diathermy. Note rapid initial rise, which was followed by a slight fall during period of heating.

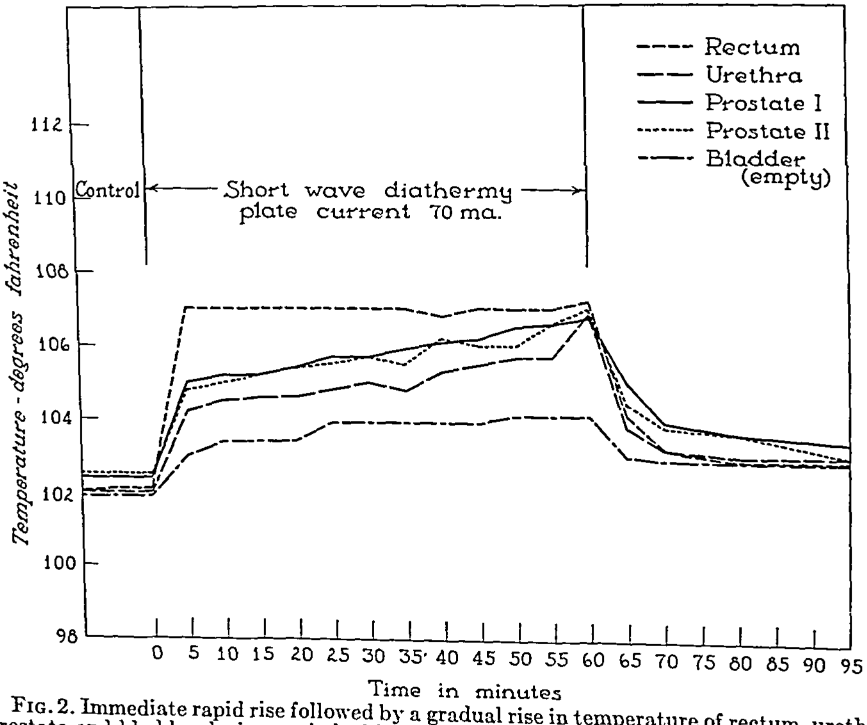

FIG. 2. Immediate rapid rise followed by a gradual rise in temperature of rectum, urethra, prostate and bladder during period of heating.

Figures 1 and 2 are representative control temperatures followed by the heating and cooling curves of the rectum, urethra, prostate and bladder. Note the rapid rise in temperature on application of diathermy.

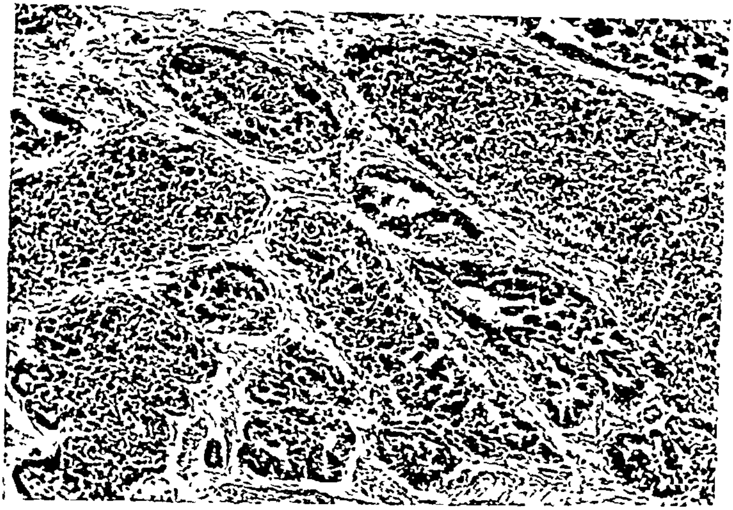

FIG. 3. Prostatic acini filled with desquamated epithelial cells

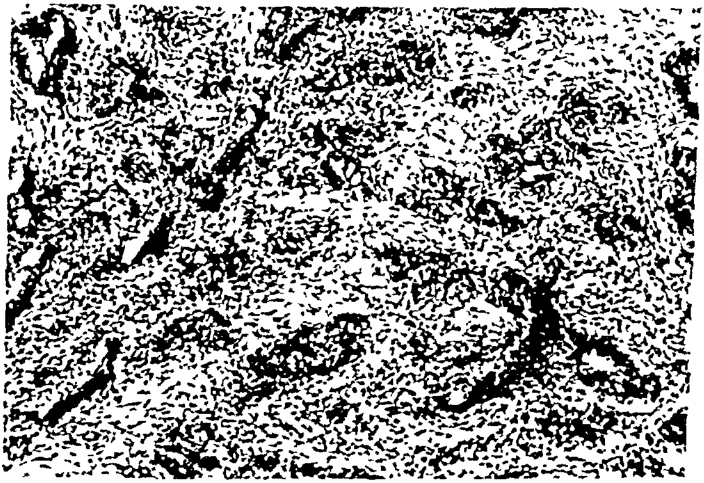

FIG. 4. Young epithelial cells lining acini and resembling those of a juvenile prostate.

HISTOPATHOLOGIC CHANGES

Comparative histologic studies were made on sections obtained from the prostate glands before and after each exposure to short wave diathermy.

No macroscopic changes were observed but the microscopic findings were of interest. It appeared that the elevation in prostatic temperature produced certain definite structural changes. These changes were characterized by desquamation of the epithelial cells which, in some cases, completely filled and blocked the acini (fig. 3).

In one dog, which was killed on the fourth day after exposure to short wave diathermy, the acini were small and did not contain mucus. The epithelial cells appeared juvenile and the entire gland resembled that of a puppy in which the acini were in an early developmental stage (fig. 4).

SUMMARY

A study was made of the temperatures developed in the prostate gland of the dog as a result of exposure to short wave diathermy by means of the rectal applicator.

The following are the pertinent findings:

Temperatures from approximately 2.5 to 6.5F above the control were recorded in the substance of the prostate within the first 10 minutes during the period of exposure to short wave diathermy.

The rectal temperatures were between 0.5 and 2.5F higher than those recorded in the prostate.

The elevation in temperature was not uniform throughout the substance of the prostate. There was consistently a greater rise in temperature in the portion of the prostate proximal to the rectum than that distal. The temperature recorded in the prostatic urethra did not prove to be a reliable index of the temperature within the substance of the prostate.

The higher temperatures developed in the prostate led to microscopic changes characterized by desquamation of the epithelial cells lining the acini.

ADDENDUM

The original purpose of this investigation was to make a comparative study of the temperature produced in the prostate gland by short wave and by microwave diathermy. A large number of carefully conducted experiments were performed using the portable microtherm and the experimental internal director furnished by the Raytheon Manufacturing Co. Satisfactory heating of the prostate gland was produced but in many instances the rectal mucosa was burned even when minimal output of the microtherm was employed. A careful investigation of this complication indicated that these burns were caused by capacitative currents generated between the two sides of the slot in the internal director. The plastic cover usually used to prevent capacitative currents was inadequate in this instance. This defect is being corrected by proper modification of the present design of internal director and, as soon as a flawless director is provided, the comparative aspect of this study will be resumed.

REFERENCE

HIBBS, D. K. AND OSBORNE, S. L.: Short wave diathermy in chronic prostatitis. Am. J. M. Sc., **201**: 547, 1941.

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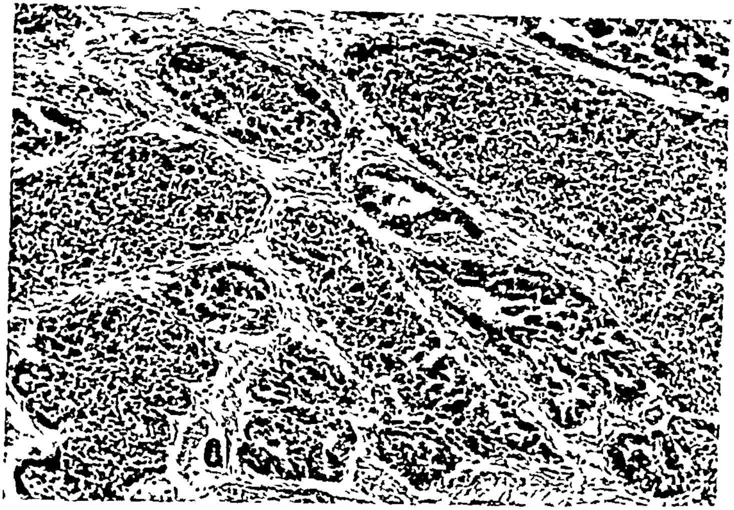
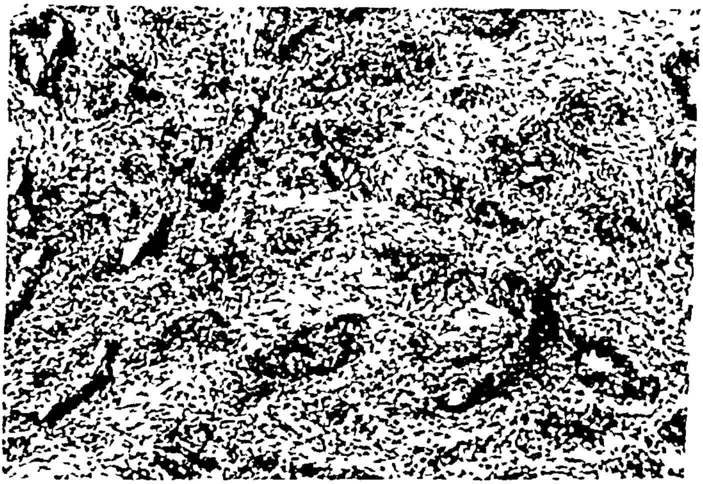


Fig. 3. Prostatic acini filled with desquamated epithelial cells



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Temperatures from approximately 2.5 to 6.5F above the control were recorded in the substance of the prostate within the first 10 minutes during the period of exposure to short wave diathermy.

The rectal temperatures were between 0.5 and 2.5F higher than those recorded in the prostate.

The elevation in temperature was not uniform throughout the substance of the prostate. There was consistently a greater rise in temperature in the portion of the prostate proximal to the rectum than that distal. The temperature recorded in the prostatic urethra did not prove to be a reliable index of the temperature within the substance of the prostate.

The higher temperatures developed in the prostate led to microscopic changes characterized by desquamation of the epithelial cells lining the acini.

ADDENDUM

The original purpose of this investigation was to make a comparative study of the temperature produced in the prostate gland by short wave and by microwave diathermy. A large number of carefully conducted experiments were performed using the portable microtherm and the experimental internal director furnished by the Raytheon Manufacturing Co. Satisfactory heating of the prostate gland was produced but in many instances the rectal mucosa was burned even when minimal output of the microtherm was employed. A careful investigation of this complication indicated that these burns were caused by capacitative currents generated between the two sides of the slot in the internal director. The plastic cover usually used to prevent capacitative currents was inadequate in this instance. This defect is being corrected by proper modification of the present design of internal director and, as soon as a flawless director is provided, the comparative aspect of this study will be resumed.

REFERENCE

Hibbs, D. K. and Osborne, S. L.: Short wave diathermy in chronic prostatitis. Am. J. M. Sc., 201: 547, 1941.

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EXPERIMENTAL STUDY OF SOLVENT ACTION OF VERSENE ON URINARY CALCULI

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The surgical treatment of urinary calculi is one of the most serious and perplexing problems in the entire realm of medicine. Medical history is replete with numerous articles on the prevention of the formation of urinary calculi and the non-surgical treatment of the condition. The various methods and procedures designed to effect dissolution of urinary calculi "in vivo" have in general failed in this purpose. In a few instances, dissolution or disintegration of urinary calculi have been accomplished by various methods.[1]

Keyser has made an extensive study of the dissolution and disintegration of urinary calculi in vitro by irrigation with various inorganic acids, solvents or reagents with varying degrees of success. He also studied the effect of some organic acids and solutions upon the dissolution of urinary calculi (table 1). His observations revealed that most of the inorganic and organic acid or reagents were effective in producing prompt surface dissolution of most alkaline stones and that at this stage the calculus was found to be covered by a mucinous organic substance which interfered with further action of the solvent. He used various ferments, i.e., urease, pepsin, diastase, trypsin and papaya to dissolve or destroy this gelatinous organic envelop and to enhance further action of the inorganic and organic solvents. Urease was found to be the most effective enzyme in dissolution of urinary calculi in vitro and in vivo.

It soon became apparent to the authors that the ideal solvent for urinary calculi in vitro and in vivo would be an agent or solution of either an inorganic or organic chemical nature which would possess the properties of dissolving most inorganic constituents (and perhaps some of the organic constituents) of urinary calculi and at the same time have the power of hydrolyzing or dissolving proteins, alkaline metal proteinates, etc. The search for such an agent invoked a study of the various chemicals employed commercially for the purposes of sequestration, chelation, dispersion, etc. After considerable study it was decided to test the efficacy of versene in the dissolution of urinary calcuil. This compound

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Read at annual meeting, American Urological Association, Washington, D. C., June 1, 1950.

[1] 1) Crowell (1924): Dissolution of cystine calculi by alkalinization of the urine and irrigation of the kidney with alkalies.
2) Randall (1932): Treatment of alkaline encrusted cystitis and dissolution of small bladder calculi by irrigations of 1 per cent phosphoric acid.
3) Keyser (1932): Dissolution and disintegration of a renal calcium phosphate calculus by irrigation of the kidney with dilute aqua regia and by acidifying the patient's urine with acid diet and dilute aqua regia by mouth.
4) Higgins (1935): Dissolution of alkaline earth stones by acid ash diet, acidifying drugs and large doses of vitamins A and D. A few acid stones were dissolved by an alkaline ash diet and alkalinizing drugs.
5) Albright, Suby and Sulkowitch (1939): Dissolution of complex alkaline earth phosphate and carbonate calculi by irrigation of the kidney with citric acid mixtures, i.e., citrate buffer solutions (Albright), solutions G and M (Suby).
6) Keyser (1942): Retrograde dissolution of calculi with ferments (enzymes), and citrate solution G.

appeared to possess the highest efficiency as a solvent of the usual inorganic salts found in urinary calculi, and was a hydrolyzing agent of various protein compounds and thus offered the greatest promise as a solvent of urinary calculi. The present study represents the first effort to test the efficacy of any organic sequestering and chelating compound in the dissolution of urinary calculi.

In the field of industrial chemistry, special attention has recently been focussed on the subject of sequestering and chelating agents particularly as applied to "softening" of water and correction of "boiler water imperfection."

The difference between complexing, sequestration and chelating is essentially a matter of chemical structure. A complex is any material which will inactivate a metallic ion. The most common complexing agents are ammonia, cyanide, citrates and tartrates. All sequestering and chelating agents are always complexing agents but all complexing agents may or may not be sequestering or chelating agents.

TABLE 1 *Study of effect of various solvents on urinary calculi (6 hour treatment) by Scherer, Claffey and Keyser)*

SOLVENT	% DISSOLUTION	ORDER OF EFFICIENCY
a Citrate buffer (Albright)	12.50	2
b G solution (Suby)	12.60	1
c 1% citrate solution	0.54	9
d Phosphate buffer	1.00	8
e 1% tartaric acid	3.15	5
f. 5% tartaric acid .	1.12	7
g 1% metaphosphoric acid	0.09	10
h Benzoic acid (saturated)	8.50	3
i 1% disodium phosphate	6.60	4
j 1% dihydrogen potassium phosphate	1.40	6

Sequestration is the ability to form soluble non-ionic complexes which are undissociated and do not possess a heterocyclic ring structure. According to Daugherty, sequestration is the reduction in concentration of a multivalent positive ion in solution by combination with a negative ion to form a complex negative ion to the extent that the remaining concentration of multivalent positive ions is insufficient to be precipitated by a given negative ion with which it has a low solubility production. The multivalent positive ion usually disappears from solution by removal as a precipitate, but may also be removed by deposition as an element or evolution of a gas. Thus a sequestering agent is any compound which will inactivate a metallic ion and at the same time keep it in solution. Ammonia, cyanide, versene, triglycine and hexametaphosphate are sequestering agents.

In Webster's Chemical Dictionary, chelation is defined as the chemical process by means of which a group or compound possessing two valences, i.e., principal or residual or both, attaches itself to a central metallic atom so as to form a heterocyclic ring structure within the molecule. Thus a chelating agent is a compound which has the ability to form soluble non-ionic compounds with polyvalent metal ions whose properties are completely changed in solution. The chelated metallic ions can no longer be precipitated from solution by the usual precipitating agents. Dimethyl glyoxine, cupferron, triglycine and versene are examples of chelating agents. In most cases, the chelating compounds are very insoluble and their primary use in the past has been as organic precipitating agents. The presence of a heterocylic ring structure in the chelating agent serves to distinguish the process of chelation from sequestration.

As early as 1833, Thomas Graham, the British chemist and founder of colloid chemistry, discovered a new complex form of phosphate, i.e., sodium metaphosphate, which is a glossy or amorphous compound having the empirical formula—$NaPo_3$—with a molecular ratio of 1 Na_2O:1 P_2O_5. In 1849 Fleitman considered the compound to be a hexametaphosphate. In 1929 Hall and Jackson first used this chemical commercially for the treatment of impurities and precipitates in boiler water and in 1932 Hall employed the compound to soften water without formation of precipitates and without removal of the "hardness" constituents. Other inorganic and organic sequestering agents containing phosphorus have been described; viz., (a) crystalline sodium pyrophosphate $Na_4P_2O_7$ or $Na_2H_2P_2O_7$, (b) crystalline sodium tripolyphosphate $Na_5P_3O_{10}$ and (c) sodium phytate $C_6H_6(Na_3PO_4)_6$—inositol hexaphosphate.

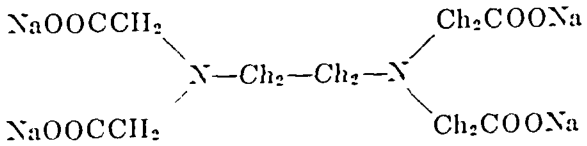
In 1938 Enders prepared and investigated the properties of two new sequestering and chelating agents which were organic compounds devoid of phosphorus. The first was designated as Trilon A, i.e.-$N\ (Ch_2CooNa)_3$ and the second, Trilon B, which is also known as the sodium salt of ethylene diamine tetra acetic acid or sodium salt of ethylene bisimino-diacetic acid. The latter substance is better known in this country as versene which is the registered trademark of the Bersworth Chemical Co., Framingham, Mass., who are manufacturers of this synthetic polyaminoacid and its sodium salts.

Although this substance has attained widespread industrial use, it has received very little attention in chemical and physiological textbooks and reviews. The various complex salts of this chelating agent were prepared by Pfeiffer and his coworkers in 1942, and Brintzinger et al. in 1942 and 1943. The acid-base properties and the equilibrium constants with hydrogen ion and with various metal ions have been investigated by Schwarzenbach and his coworkers in 1947 and 1948.

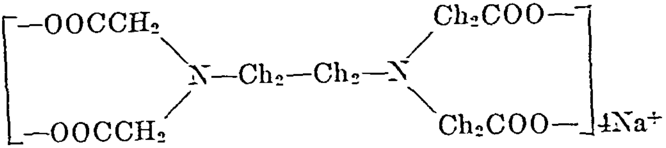
CHEMISTRY OF VERSENE

Information concerning the chemical formula, reactions and properties of ethylene diamine tetra acetic acid and its sodium salts has been supplied by A. E. Martell, R. C. Plumb and F. C. Bersworth of the Bersworth Chemical Co., Framingham, Mass., and by J. J. Singer, chief chemist of this company.

Versene is the aqueous solution of the tetra sodium salt of ethylene diamine tetra acetic acid. The chemical structure of this compound is usually represented as



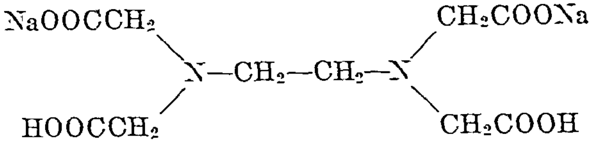
Since this is a salt of a strong base, it is completely ionized in solution. Consequently its structure may also be represented by



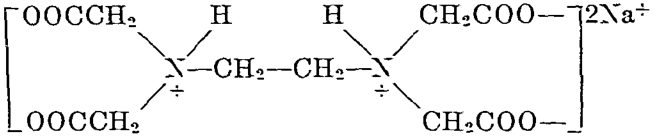
For practical purposes, this formula may be contracted to Na_4Ve.

$$Na_4Ve \underset{OH^-}{\overset{H^+}{\rightleftarrows}} Na_3HVe \underset{OH^-}{\overset{H^+}{\rightleftarrows}} Na_2H_2Ve \underset{OH^-}{\overset{H^+}{\rightleftarrows}} H_4Ve$$

The sodium salt may be easily crystallized from water solution as a hydrate. Its structure is represented by



It has been definitely shown that the sodium in the bisodium salt is completely ionized in solution. It is also known that the two basic nitrogen atoms are in a position which is alpha to the carboxyl groups and that such groups exist in the form of "zwitter ions". Consequently the structure for this disodium salt may be written as



The sodium and other alkali metal salts of ethylene diamine tetra acetic acid are quite soluble in water. The acid itself is very insoluble. Thus the addition of any strong acid to a solution of a salt of versene results in the formation of a crystalline precipitate of the acid. For convenience the various salts and the acid may be called tetra sodium versene, disodium versene, versene acid, etc.

COMPLEX FORMATION OF METAL IONS WITH VERSENE

When a divalent metal ion, i.e., calcium ion, forms a complex with versene salts, the metal becomes coordinated with versene anion as indicated in following equation:

$$Ca^{++} + Na_4Ve \rightarrow Na_2\,[CaVe] + 2\,Na^+$$

In this manner, the calcium salt is bound up in a non-ionic complex with versene. A considerable drop in pH occurs when a neutral calcium salt, i.e., calcium chloride is added to a solution of disodium salt of versene. This is due to the liberation of hydrogen ions in the course of complex formation:

$$Ca^{++} + Na_2H_2Ve \rightarrow Na_2\,[CaVe] + 2\,H^+$$

Thus the solution undergoes a considerable drop in pH and an equilibrium is reached.

It is important to bear in mind that the formation of acid in the course of the complex formation of metal salts with versene predicts the pH stability of versene complexes. The addition of acid to a solution of versene complex would obviously reverse the equilibrium indicated in the above equation. Hence it is readily apparent that all versene complexes become less stable as the pH is reduced and show maximum stability at high pH. This fact has an important bearing on the various applications for versene.

It is important to note that most versene complexes are produced in solution in the form of their alkali-metal salts and hence are quite soluble. The metal ion undergoing complex formations is also tied up in a non-ionic form and hence will not precipitate even in the presence of negative ions which usually precipitate such a metal. It is also known that alkaline versene solutions will dissolve precipitates of many metals even though such precipitates usually have a maximum insolubility in bases. This is indicated in the following equations:

Calcium phosphate

$$Ca_3(Po_4)_2 + {}_3Na_4Ve \rightarrow {}_3Na_2\ (CaVe) + {}_2Na_3Po_4$$

Calcium oxalate

$$CaC_2O_4 + {}_3Na_4Ve \rightarrow Na_2\ (CaVe) + Na_2C_2O_4$$

Magnesium carbonate

$$MgCo_3 + No_4Ve \rightarrow Na_2\ (MgVe) + Na_2\ Co_3$$

The chelating or sequestering power of versene with ions of heavy metals, i.e., copper, nickel, cobalt, etc. is in general much stronger than with the alkaline earth metals listed above. It is also known that most metals are strongly sequestered above a pH of 5, while the heavy metals may be sequestered even at somewhat lower pH values. The higher the pH, the greater is the chelating power of versene with a particular metal.

APPLICATION

The uses of sequestering agents in general have been described by Daugherty in 1948. Although versene and its alkali metal salts have most of the properties of ordinary sequestering agents, it differs in many respects and is more properly called a chelating agent.

It is interesting to compare versene, a complex unnatural synthetic polyaminoacid with hexametaphosphate, a common type of inorganic sequestering agent. Martell, Plumb and Bersworth pointed out that the sequestering action of hexametaphosphate is due to some extent to the dispersion action of the reagents. Thus the precipitation of alkaline earth ions is prevented because the dispersing action of the finely divided precipitate tends to prevent coagulation of the suspended material. Coagulation gradually takes place as the polyphosphate reverts to orthophosphate in the presence of water, thus precipitating the alkaline earth metals.

Versene and its sodium salts differ in that they react directly with a metal cation and form a stable soluble reaction product, i.e., the chelate of the metal. Such chelates are quite stable over a wide pH range. In most cases, they are not decomposed by either weakly acid or highly alkaline solutions. Temperature, time and addition of common precipitation agents have no effect on metal ions so chelated. This metal chelate, being a product of a definite chemical reaction, requires a specific amount of chelating agent to obtain the desired result. Insufficient amounts leave some unreacted metal ions and such residual ions can be precipitated.

It is clear from the facts presented that chelating agents find their greatest use in the treatment of alkali metal salts since the chelating power increases as the pH rises.

Applications of this unusual chelating power of versene has been made in the following commercial, industrial and hygienic fields.

1) Its most obvious use is in the general field of water softening.

2) This function may be utilized in detergent mixtures, clarification of soap, and removal of trace metal ions, which act as pro-oxidants of soaps, fats and oils.

3) It has a distinct use in the hydrolysis and dissolving of proteins, metal proteinates or other metal compounds in which the metal exists either as a simple or complex salt.

4) The "reserve" alkalinity of tetra sodium salt of versene is very useful in certain chemical reactions, i.e., (a) direct addition of this salt to a fat results in saponification and formation of a soap containing the alkali metal salt of versene, (b) similar reactions may be carried out with numerous organic and inorganic compounds to produce solutions with controlled composition and pH.

5) This compound has been used in different industries, i.e., rubber (natural and synthetic), dye, textile, flotation, separation of metals, paints, varnishes, stabilizers for plastics, etc.

TOXICITY OF VERSENE AND ITS SALTS

An increasing amount of studies on the toxicity of Versene are becoming available. From the evidence at hand, versene is no more toxic than any other alkaline solution of equal pH. In regard to pH, the tetra sodium salt has a relatively high pH, tri-sodium and disodium salts have correspondingly lower pH depending on the number and degree of ionization of the hydrogen atoms.

The following reports are significant:

1) The Bersworth Chemical Co. has not observed any ill effects in the plant personnel over a 10 year period during which time intensive production of very large quantities of versene and its derivatives, ranging in pH from 3 to 13, was carried out.

2) The same compounds have been used in industry and research in large amounts and in formulated proprietary products without complaint of any kind.

3) Patch tests with versene at pH 7 and 8.5 applied at 0.50 per cent concentration shows no irritating effects.

4) Intradermal injections of 2 per cent neutral sodium salt of versene and castile soap in physiological saline solution was not injurious to test animals. Control animals injected with soap and saline solution only showed that the triple combination is no more irritating than the control.

5) Oral feeding tests have been carried out by Dr. Martin Rubin, Georgetown Medical School, Washington, D. C. Versene was fed in drinking water to large

groups of rats for a period of 1 year at dose levels of approximately 2 to 5 per cent of total food and water intake, i.e., 12.5 mg. of versene per ml. All test rats gained weight with no fatalities or signs of toxic effect. These experiments are being continued for longer periods to establish the toxicity limits under conditions more closely conforming to potential utilizations in food and beverages.

6) The effect of parenteral injection of tetra sodium salt of versene was studied by Dykerkoff and coworkers who found that parenteral injection of 80 mg./kg. produced no toxic effects in rabbits. Tetany was noted at 125 mg./kg. but recovery followed injection of 7 mg. calcium in the form of calcium chloride. Rubin found that versene is absorbed by the systemic route and exerts its calcium depressing action rapidly in the case of intraperitoneal injection being 100 per cent fatal at a dose of 100 mg./kg. Versene is absorbed more slowly from intramuscular sites and least rapidly from subcutaneous sites.

7) Rubin studied the effects of the intravenous administration of purified versene (100 mg./kg., pH 7.2) in rabbits. When the solution was injected rapidly, i.e., within 15 seconds, it was found that at lethal doses of versene the blood level falls precipitously and the animals die in convulsive tetany. The results obtained after the rapid injection are indicated in the following table.

Dose, mg./kg.	*% Survival*
100	0
50	0
25	10
15	60
12.5	80
10	100
5	100

When the intravenous injection was extended over a period of 10 minutes at a dose level of 50 mg./kg., the survival rate was 100 per cent with little change in the available calcium levels. Administration of intravenous infusion over a period of 3 hours allowed the introduction of 2000 mg./kg. of versene before the available calcium was depressed to a level incompatible with life.

When versene was administered intravenously to rabbits in 5 mg./kg. daily doses for 30 to 60 days, there were no significant changes in the blood calcium levels, no evidence of cumulative toxicity and no histologic evidence of damage to the liver, kidney, adrenal or other organs. Rubin found that the calcium complex of versene is virtually nontoxic by any route of administration. Dosages of 750 mg./kg. injected intravenously to rabbits showed 100 per cent survival.

Rubin concluded that the toxicity of versene to animals is due to its function in binding calcium, and that its acute toxicity may be minimized by the slow administration of the agent which allows for replacement of calcium in the blood circulation by the labile reserves of the animal. He is of the opinion that versene will be found acceptible for human use as an adjunct in the processing of drugs, foods and beverages.

EXPERIMENTAL STUDY

Any experimental investigation of the physical properties and chemical composition of urinary calculi entails many complex and time consuming studies.

The present study of solvent action of versene upon urinary calculi may be divided as follows:

1) Study of calculi.
    a. identification, i.e., chemical composition.
    b. preparation, i.e., dehydration, sawing, sealing.
2) Solvent action of versene upon calculi in vitro.
    a. preparation of versene solutions.
    b. special irrigation apparatus for solubility studies.
3) Study of toxic action of various concentrations of versene.
    a. effect on the lining membrane of renal pelvis, ureter and bladder.
4) Solvent action of versene on calculi in vivo.
    a. stones placed in dilated pelvis of experimentally produced hydronephrosis.

TABLE 2. *Crystalline components of urinary calculi as determined by spectographic and x-ray diffraction methods by Prien and Frondel*

CRYSTALLINE COMPONENTS	FORMULA	MINERALOGICAL NAME
Calcium oxalate monohydrate	$CaC_2O_4 \cdot H_2O$	Whewellite
Calcium oxalate dihydrate	$CaC_2O_4 \cdot 2H_2O$	Weddellite
Magnesium ammonium phosphate hexahydrate	$MgNH_4PO_4 \cdot 6H_2O$	Struvite
Carbonate-apatite	$Ca_{10}(PO_4CO_3OH)_6OH_2$	Carbonate-apatite
Hydroxyl-apatite	$Ca_{10}(PO_4)_6(OH)_2$	Hydroxyl-apatite
Calcium hydrogen phosphate dihydrate	$CaHPO_4 \cdot 2H_2O$	Brushite
Uric acid	$C_5H_4N_4O_3$	
Cystine	$SCH_2CH(NH_2)—COOH$	
Sodium acid urate	$NaHC_5H_2O_3N_4H_2O$	
*Tricalcium phosphate	$Ca_3(PO_4)_2$	Whitlockite
†Indigo	$C_{16}H_{10}N_2O_2$	
†Xanthine	$C_5H_4N_4O_2$	

* Not found but identity established.
† Not found but identity acceptable.

Study of calculi. It is readily apparent that the dissolution of a specific calculus is directly dependent upon its chemical composition. Various methods of determining the qualitative composition of calculi have been devised. We are greatly indebted to Jensen (1939) and Prien (1941) for their application of modern analytical techniques of mineralogy to the identification of the crystalline components of calculi. Utilizing the polarizing (petrographic) microscope and x-ray diffraction techniques, in a study of 700 calculi, Prien and Frondel found only 9 distinct crystalline substances to be present in calculi as indicated in table 2.

They showed that many supposed crystalline components of calculi recorded in the urological literature by many investigators are actually nonexistent as determined by modern physical methods of identification. Their studies served to emphasize the inadequacies of the qualitative chemical analysis routinely employed in most clinics throughout the world. They also showed that the wide discrepancies exist between the results of analysis of calculi by modern physical methods and those obtained by simple qualitative chemical analysis and attribute these differences to 1) indeterminate nature of the reactions in many of the procedures used in chemical tests, 2) invalid reactions resulting from interference by organic substances of unknown composition, 3) the complex chemical structure of many crystalloids present in calculi, particularly the phosphates and oxalates, and 4) the small size of many calculi often prevents a complete chemical examination. The one and only objection to the routine use of polarizing microscopic and x-ray diffraction technique in the analysis of stones is that these methods require costly apparatus and specially trained technicians who are not available in every hospital and city.

TABLE 3. *Classification of 124 calculi studied by the authors*
A—Chemical composition determined by physical methods by Prien
B—Chemical composition determined by qualitative chemical methods by authors

CHEMICAL COMPOSITION OF CALCULI	NO. OF CALCULI	
1. Uric acid	3 A	
2. Uric acid, calcium oxalate	1 A	
3. Uric acid, calcium, magnesium, ammonium oxalate, xanthin		1 B
4. Uric acid, calcium, magnesium, oxalate, phosphate	1 A	
5. Uric acid, calcium magnesium, phosphate	1 A	
6. Cystine	1 A	
7. Cystine, apatite	1 A	
8. Calcium oxalate	6 A	1 B
9. Calcium, ammonium oxalate	1 A	
10. Calcium, magnesium oxalate		1 B
11. Calcium, magnesium, oxalate phosphate	1 A	
12. Calcium, magnesium, oxalate, sulfate	1 A	
13. Calcium carbonate	2 A	
14. Calcium ammonium carbonate		1 B
15. Carbonate apatite	1 A	
16. Calcium monohydrate, apatite	1 A	
10. Calcium, magnesium, carbonate, phosphate	1 A	
18. Calcium, magnesium, ammonium, carbonate, phosphate *and oxalate*	2 A	
		96 B
	24 A	100 B

The authors are cognizant of the failings and inadequacies of qualitative chemical analysis of calculi. However since the necessary apparatus and technicians to carry out the physical methods of analysis were not available in Baltimore, we were forced to reply on qualitative chemical tests to determine the composition of the calculi employed in this study with the exception of 24 calculi contributed by Dr. E. L. Prien.

In a study of 700 calculi, Prien and Frondel found only 9 distinct crystalline substances present.

Identification of calculi (table 3): In the series of 124 calculi studied by the authors, the chemical composition of 24 stones had been previously determined by Prien by physical methods. The chemical composition of the remainder (which were taken from the collection of calculi in the Pathological Department of Sinai Hospital or from the Brady Urological Institute of the Johns Hopkins Hospital through the courtesy of Drs. W. W. Scott and W. E. Goodwin) was determined by employing the schema for qualitative analysis proposed by Scherer, Claffey and Keyser in 1945 with some minor modifications.

In this experimental study each calculus was sawed into two parts and the saw dust used for analysis as a representative sample of all material in the calculus. In the case of a concentric laminated calculi, a sample was obtained from each layer separately, powdered in a mortar and analysed separately. Small calculi were powdered in toto and analysed. Each stone was tested for the presence of organic matter and then subjected to the following individual tests, viz., uric acid and urates, xanthine, cystine, urostealith. The following tests were also performed; viz., calcium, magnesium, ammonium, phosphates, carbonates and oxalates.

Preparation of the calculus: After the qualitative analysis of the stone was completed, each half of the stone was dried at 105 C for ½ to 1 hours, the stone being weighed before and after drying. The freshly cut surface of each part was coated with a thin layer of DeKhotinsky cement in order to prevent the penetration of the solvent through the cut surface. Only in this manner could the conditions prevailing in the uncut stone be duplicated. The stone was again weighed after application of the cement.

The effect of dehydration upon the weight of the calculi was studied. Five calculi were placed in drying oven at 105 C for varying periods of time. It was found that after ½ hour there was an average loss of 10 per cent; after 1 hour an average loss of 15 per cent and after 1½ hours an average loss of 16 per cent. No further appreciable loss was observed after 2 hours and up to 6 hours.

Study of solvent action of versene upon the calculus (fig. 1): A special apparatus was employed for continuous irrigation of the stone with the versene solution. This apparatus was designed by Mr. Thomas Hofmaster, research laboratory technician at the Sinai Hospital, and is a simple and efficient apparatus which can easily be constructed in any laboratory. The apparatus consists of:

A. Reservoir containing versene solution is a 500 cc flask with a narrow mouth occluded by a rubber stopper with three holes through which three (¼ in.) glass tubes are inserted. One tube transmits the versene to the irrigation apparatus by gravity; a second tube is connected to a vacuum apparatus, (V), not shown in drawing, and the third tube draws irrigating fluid up from the collecting receptacle back into the reservoir.

B. Clamp used to regulate the rate of flow (10 cc per minute).

C. Murphy drip mechanism.

D. Stone chamber consists of a discarded stainless steel blood filter and has numerous fine openings to permit constant contact of versene with the stone.

E. The prepared stone.

F. Thermoregulator to control the temperature of the water bath which is usually maintained at 37.4 C.

G. A long glass tubing ($\frac{1}{4}$ in.) diameter whose lower end is bent to hold the stone chamber in position within the irrigation chamber, thus permitting continuous irrigation of the stone.

H. An electric hot plate on which is placed water bath (500 cc pyrex flask) for immersion of the irrigation chamber.

J. Irrigation chamber constructed in the laboratory of large glass tube with closed end measuring 10 cm. in length by 3 cm. in diameter. An outlet tube is fused in the midportion to permit the escape of the irrigating fluid into receiving receptacle which is a glass beaker 100 cc from which the fluid is drawn back by vacuum into the reservoir to be used over again.

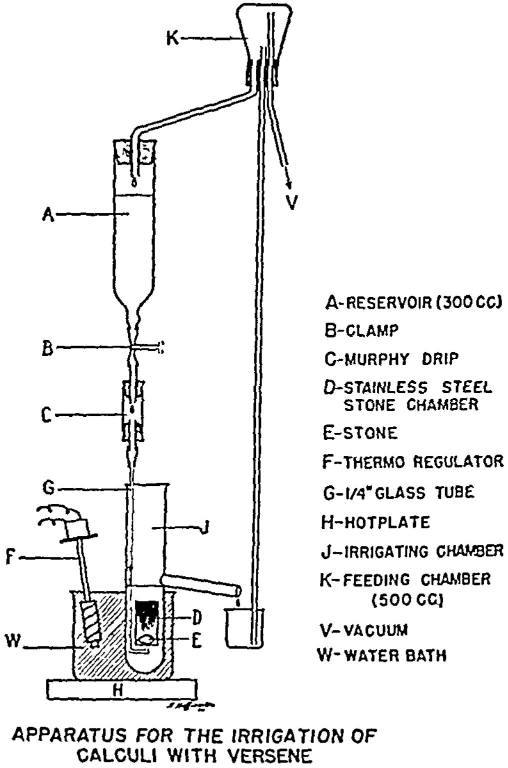


Fig. 1. Apparatus for irrigation of stones with versene

K. Glass feeding chamber—composed of a long glass chamber (300 cc) with tapering outlet which is connected by a rubber tubing to the Murphy drip mechanism.

After the desired period of irrigation with versene solution the calculi were washed with distilled water until free from versene solution and salts. The calculus was dried again at 105 C for $\frac{1}{2}$ to 6 hours and the loss in weight was recorded as per cent dissolution.

Preparation of versene solution: The versene solution was prepared in 0.5, 1, 2, 5, 10, 12.5, 15, 20 and 50 per cent solutions by adding the required amount of purified versene powder to 100 cc of sterile distilled water. To each solution, enough sodium hydroxide (NaOH-10 per cent solution) was added to bring the pH to 7.2 as determined by Lamotte pH indicators or by electrometric methods. Accurate measurment of the pH should be made with a pH meter utilizing a glass electrode when this apparatus is available. This method was employed for the preparation of the solutions in the in vivo studies. Determination of pH by special litmus paper is not sufficiently accurate to warrant its use.

The last step is sterilization of the alkaline versene solution by autoclave at the standard pressures used in the operating room.

Preliminary study of solvent action of versene. The preliminary study consisted of testing the solubility of several different calculi of various chemical compositions in versene solutions of different concentrations, i.e., 0.5, 1, 2, 5, 10, 20 and 50 per cent. A small calculi of known weight was placed in 5 cc of each of the different concentrations of versene solution for 1 to 24 hours. The calculi were weighed after such treatment and the difference in weight recorded as per cent of dissolution. An analysis of the data (fig. 2) of this specific study revealed:

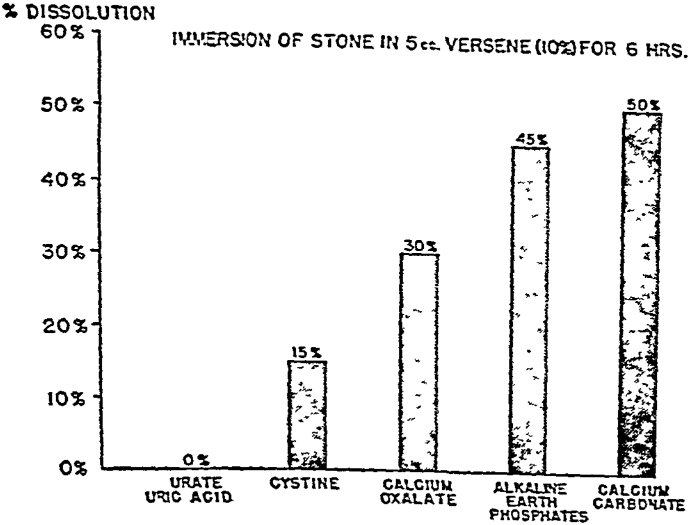


FIG. 2. Illustrating amount of dissolution of urinary calculi following immersion of different calculi in 5 cc versene (10 per cent) for 6 hours.

1) The most effective solvent action is observed with the 10 per cent solution of versene. The chelating action of 10 per cent versene was essentially the same as 15 per cent and 20 per cent versene solution.

2) Uric acid and/or urate stones are not affected by versene solution in various concentrations.

3) Calcium carbonate calculi were dissolved more readily than other calculi, i.e., 51.5 per cent dissolved in 6 hours with 10 per cent versene solution.

4) Mixed alkaline earth phosphatic calculi had a high ratio of solubility, i.e., about 45 to 50 per cent dissolution in 6 hours with 10 per cent versene solution.

5) Calcium oxalate in pure or combined forms are less readily dissolved, i.e., 31.1 per cent in 6 hours with 10 per cent versene solution.

6) Cystine calculi exhibited a 15 per cent dissolution in 6 hours.

Experimental study of the dissolution of calculi by irrigation with versene solution. This study consisted of subjecting 120 different calculi to irrigation with different concentrations of versene over varying periods of time. The majority of the calculi studied were composed of calcium, ammonium, magnesium, phosphate, carbonate and oxalate which represents the usual type of mixed stone encountered in our practice as well as in the practice of others in this country. The calculi were carefully dried and weighed before and after irrigation with versene solution and the loss of weight recorded as per cent dissolution.

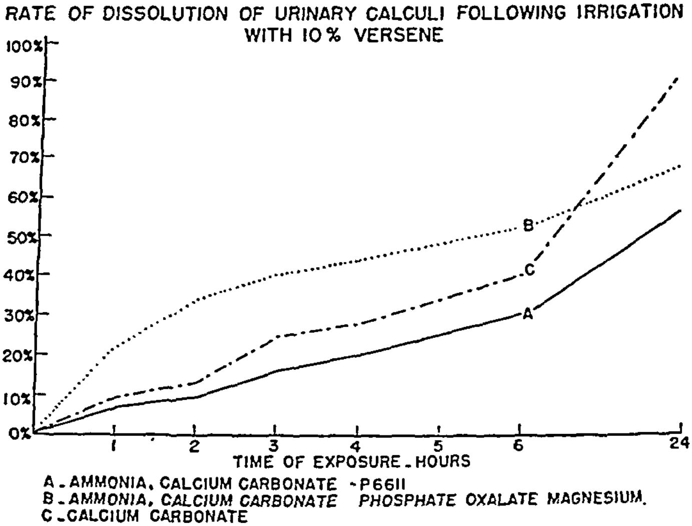


FIG. 3. Showing rate of dissolution of calculi following irrigation with 10 per cent versene over a period of 24 hours.

Analysis of the results of these experiments revealed:

1) A very high rate of dissolution was obtained with 10 per cent versene solution which only differed by ±2 per cent from a 15 per cent or 20 per cent versene solution.

2) There was a progressive increase in per cent of dissolution of such calculi following continuous irrigation with 10 per cent versene solution. The following results represent the average loss (per cent of dissolution) at the end of specific time intervals, viz.,

30 minutes	10-12%
1 hour	20-25%
2 hours	35-45%
4 hours	50-60%
18 hours	60-65%
24 hours	78-80%
48 hours	88-100%

The graph (fig. 3) shows the results of irrigation with 10 per cent versene over a period of 24 to 48 hours.

Experimental study of toxic action of 10% versene solution upon the mucosa of the renal pelvis, ureter and bladder. A. Continuous irrigation of the bladder of 4 rabbits with 10 per cent versene (buffered to pH of 7.2 with 10% NaOH) through a No. 16 double irrigating Foley catheter over a period of 4 hours disclosed moderately severe irritative changes on gross examination. Histological studies also revealed superficial and deep changes in the mucosa or submucosa.

B. Irrigation of the renal pelvis of 6 dogs with 10 per cent versene revealed moderately severe irritative action on gross and microscopic examination. This study was carried out in three experiments, viz.,

1) Retrograde catheterization of the normal ureter in large dogs (4 F catheter).
2) Retrograde catheterization of the normal undilated pelvis and ureter through a cutaneous ureterostomy (6 F double lumen catheter).
3) Retrograde catheterization of the dilated renal pelvis and ureter, i.e., resulting from partial constriction of the lower ureter by ligatures or surrounding the lower end of ureter. A 6 F double lumen catheter passed up through the ureterocutaneous opening.

Practically the same percentage of dissolution was obtained with weaker solutions of versene, i.e., 7.5, 5 and 3 per cent with a pH of 7.2, with correspondingly less irritation. The degree of irritation was decidedly less when $NaHCO_3$ was employed instead of NaOH as the alkalizing agent.

Experimental study of the dissolution of calculi "in vivo". Unilateral dilatation of the pelvis and ureter was produced 1) by partial constriction of the ureter by ligature or 2) by placing a one inch piece of polyethylene around the lower ureter. After a period of 14 to 21 days, the renal pelvis was exposed and incised and a small calculus i.e., mixed alkaline earth, phosphate, oxalate, carbonate, was placed within the pelvis which was carefully resutured to preserve its integrity. The ureter was severed in its lowest portion, i.e., close to the site of constriction and was transplanted to the loin. A No. 6 or No. 9 double lumen catheter was passed up the ureter into the pelvis and continuous irrigation of the pelvis with 10 per cent versene was performed for 4 to 6 hours.

It was observed that 25–30 per cent dissolution of the calculus was obtained after irrigation for 4 to 6 hours but was accompanied by severe chemical irritation of the pelvis and a necrotizing papillitis. It is interesting to note that essentially the same percentage of dissolution was obtained with a 7.5, 5, and 3 per cent solution of versene (pH 7.2 with NaOH or $NaHCO_3$) with a proportionate decrease in the degree of irritation. When a 3 per cent solution of versene (pH 7.2 with $NaHCO_3$) was employed, the degree of irritation of the renal pelvic epithelium was minimum and in several cases was entirely absent.

SUMMARY

The authors have attacked the problem of the dissolution of calculi in vitro by employing for the first time the chemical process of chelation and a new chelating agent, i.e., versene. Our studies indicate that 10 per cent versene is a particularly effective solvent in vitro for the following types of calculi, viz, calcium carbonate and mixed alkaline earth phosphates. It is also effective to a lesser degree in the dissolution of calcium oxalate calculi in pure or combined

forms. It is surprising to note that cystine calculi in pure or combined forms are also dissolved by 10 per cent versene solution. Uric acid and urate calculi are not affected by versene solution in various concentrations.

Experimental studies were undertaken to determine the toxic action of 10 per cent versene (pH 7.2) upon the lining membrane of the renal pelvis, ureter and bladder of dogs and rabbits and it was found that continuous irrigation of these structures for 4 to 6 hours produced demonstrable irritative action of the epithelial lining of the bladder, ureter and pelvis.

Experimental studies in dogs of the dissolution of calculi in vivo i.e., retrograde irrigation of hydronephrotic pelvic containing calculi reveal that approximately 25 per cent dissolution of alkaline earth phosphatic calculi after 4 hours irrigation with 10 per cent versene but was accompanied by irritation of the renal pelvis and papillae.

The authors are continuing their studies of the toxic effects of versene and its salts upon the bladder and renal epithelium. This study is still in progress but it does appear that weaker solutions of versene acid and its various salts, i.e., 3, 5, and 7.5 per cent are decidedly less irritative. Studies are also in progress to determine the influence and relation of alterations in the pH of the various versene solutions, i.e., utilizing various inorganic and organic acidifying and alkalinizing agents, upon the toxic and irritative properties of the solution. We believe that these studies will reveal the ideal strength and pH of versene to insure its chelating action without irritative action on the urinary organs.

The authors are of the opinion that this new chelating agent offers definite promise as a solvent for urinary calculi in humans. Clinical trials will be undertaken as soon as the appropriate non toxic and non irritating solution of versene is determined and substantiated by animal experiments. A subsequent report of these results will be presented at a later date.

This study has also prompted the authors to investigate the efficacy of other organic sequestering and chelating compounds in the dissolution of urinary calculi and the results of this study will be reported later.

The authors wish to express their sincere thanks to Drs. E. L. Prien, W. W. Scott and W. Goodwin who contributed some of the stones used in this study, and to Dr. Mano Golden, Thomas Hofmaster and Melvin Fuld for their invaluable technical assistance.

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REFERENCES

ALBERT, A. AND GLEDHILL, W. S.: The choice of a chelating for inactivating trace metal. Biochem. J., 41: 529, 1927.

ALBRIGHT, F., SULKOWITCH, H. W. AND CHUTE, R.: Non surgical aspects of the kidney stone problem. J.A.M.A., 113: 2049, 1939.

BRINTZINGER, H., THIELE, H. AND MULLER, U.: Copper, nickel and uranyl compounds of ethylene diamine tetra acetic acid. Ztschr. f. anorg. u. allg. chem. 249: 113, 1942.

BRINTZINGER, H., THIELE, H. AND MULLER, U.: Complex compounds and salts of ethylene diamine tetra acetic acid. Ztschr. f. anorg. u. allg. chem., 251: 285, 1943.

CROWELL, A. J.: Cystin nephrolithiasis; roentgenographic demonstration of disintegration by alkalinization. Surg., Gynec. & Obst., 38: 87, 1924.

DAUGHERTY, T. H.: Sequestration, dispersion and dilatancy; lecture demonstration. J. Chem. Ed., 25: 48, 1948.

Dykerhoff, H., Marx, R. and Ludwig, B.: Über den wirkungs mechanismus und die verwendbarkeit einiger blutgerinnung shemmender organischer substanzen. Ztschr. f. d. ges. exper. med., 110: 412, 1942.

Ender: English patent 474518 (1937). Fette. u. seifen., 45: 144, 1938.

Fleitmann, T.: Uber die verschiednen metaphosphorauren und zwei neue sauren derselben verbindungs proportion. Ann. d. physik. u. chemie, 78: 233, 328, 1849.

Graham, T.: Researches on the arseniates, phosphates and modification of phosphoric acid. Philosoph. Trans. Roy. Soc. London, 123: 253, 1833.

Hall, R. E.: U. S. Patent No. 1,956, 515 (1934), Reissue No. 19719 (1935).

Hall, R. E. and Jackson, H. A.: U. S. Patent No. 1,903,041, (1933).

Higgins, C. C.: Experimental and clinical observations on urinary calculi. New Eng. J. Med., 214: 1007, 1935.

Higgins, C. C.: Urinary lithiasis; experimental production and solution with clinical application of end results. J. Urol., 36: 168, 1936.

Hodge, I. G., Hayllar, B. L. and Way, R. A.: A new set of citrate buffers for use in urinary tract lithiasis. J. Urol., 48: 204, 1942.

Jensen, A. T. and Thygesen, J. E.: Uber die phosphat konkremente der harnwege. Ztschr. f. Urol., 32: 659, 1938.

Jensen, A. T.: On concrements from the urinary tract, II. Acta chir. scand., 84: 217, 1940.

Jensen, A. T.: On concrements from the urinary tract, III. Acta chir. scand., 85: 473, 1941.

Keyser, L. D.: Urinary lithiasis; its cause and prevention. South. Med. J., 25: 1031, 1932.

Keyser, L. D.: Newer concepts of stone in the urinary tract. J. Urol., 42: 420, 1939.

Keyser, L. D.: Urinary lithiasis; a review of a quarter century of research. J. Urol., 50: 169, 1943.

Keyser, L. D.: Studies in urinary calculosis. J. Urol., 54: 194, 1945.

Keyser, L. D., Scherer, P. C., and Claffey, L. W.: Studies in the dissolution of urinary calculi; experimental and clinical aspects. J. Urol., 59: 826, 1948.

Martell, A. E., Plumb, R. C. and Bersworth, F. C.: The properties and uses of ethylene diamine tetra acetic acid and its salts. Bulletin of Bersworth Chemical Co., Framingham, Mass., 1949.

Mellan, I.: Organic reagents in inorganic analysis. Philadelphia: Blakiston Co., 1941.

Peiffer, P. and Offerman, W.: Calcium and cooper complex salts of Trilon A and B. Berichte d. deutschen chem. gesellschaft., 75: 1, 1942; idem. 76: 847, 1943.

Prien, E. L.: The use of polarized light in the analysis of calculi and in the study of crystals in tissues; a preliminary report on the method employed. J. Urol., 45: 765, 1941.

Prien, E. L. and Frondel, C.: Composition of urinary calculi. J. Urol., 57: 949, 1947.

Randall, A.: Presention of the recurrence of urinary calculi. Am. J. Surg., 18: 482, 1932.

Rubin, M.: Personal communication.

Scherer, P. C., Claffey, L. W. and Keyser, L. D.: Dissolution of urinary calculi; A scheme for the qualitative analysis of urinary calculi. Bull. of Virginia Polytechnic Institute, 38: 1, 1945.

Schwarzenbach, G. and Ackerman, H.: Ethylene diamine tetra acetic acid. Helv. Chem. Acta., 30: 1798, 1949.

Schwarzenbach, G. and Biederman, W.: Titration of metals with ethylene diamine tetra acetic acid, H_4Y; indications of end point by pH effects. Helv. Chem. Acta., 31: 459, 1948.

Schwarzenbach, G. and Ackerman, H.: Homologues of ethylene diamine tetra acetic acid and their alkaline earth complexes. Helv. Chem. Acta., 31: 1029, 1948.

Suby, H. I. and Albright, F.: Dissolution of phosphatic urinary calculi by the retrograde introduction of a citrate solution containing magnesium. New Eng. J. Med., 228: 81, 1943.

Suby, H. I., Suby, R. M. and Albright, F.: Properties of organic acid solutions which determine their irritability to the bladder mucous membrane and the effect of magnesium in overcoming this irritability. J. Urol., 48: 549, 1942.

Versene, the modern chelating agent. Technical Bulletin No. 1, Bersworth Chemical Co., Framingham, Mass., 1949.

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DISCUSSION

DR. HOWARD I. SUBY (Boston, Mass.): I have enjoyed reading Dr. Gehres's paper very much.* There has been little question in my mind for many years that progress in stone dissolution might very well come from some judicious use of commercial water softeners.

When Dr. Albright, Dr. Sulkowitch, Dr. Rosenheim, and I started many of our studies in stone dissolution in 1939, much time was spent with experiments using calgon, sodium hexameta phosphate, a water softener which even today is regarded as one of the most efficient solvents of calcium salts. It became obvious to us than that calgon was about as effective a calcium solvent as many citric acid solutions. It also became obvious, however, that the prolonged use of calgon on bladder mucosa caused much more irritation than citrate solutions which contained magnesium. Addition of magnesium to the calgon seemed to do little or nothing to minimize irritation.

Our interest in commercial water softeners, however, did not wane and for the past 14 months at the Massachusetts General Hospital, we have done considerable experimental work with sequestrine, a substance produced by the Alrose Chemical Company of Providence, Rhode Island. This is precisely the same chemical (versene acid)—only with a different trade name, as calsol which has been utilized by Dr. Gehres. Our conclusions regarding the effectiveness and practicality of this chemical have been hopeful but far from conclusive. A preliminary report will soon be published. 1 per cent, 2 per cent and 3 per cent solutions of sequestrine have been used on rabbits' teeth and there has been little, if any, difference in the solubility effect between even the 3 per cent solution of sequestrine and solution G. We have used this solution in a large number of rabbits and in many of these there seemed to be more irritation than was seen with solution G while in others, chiefly where the 1 per cent solution was used, the bladders looked quite normal. This has kept up our interest in this product. I think it is important that one realizes that a large number of animals must be used before any sound conclusions can be drawn regarding irritability effect. We are continuing work on this problem.

Slide 1 shows the average loss in specific gravity of teeth shaken in solution G. 1 per cent sequestrine, 2 per cent sequestrine, and 3 per cent sequestrine for 8 hours. It also suggests that the solutions are less effective at pH 7.0 than 4.2. We believe that these figures give us quite an accurate comparison in the effectiveness of these solutions in dissolving calcium phosphate stones. Our results using sequestrine solutions on calcium oxalate stones have not as yet been encouraging. In urate stones I believe that perhaps some of Dr. Gehres's good results may have been due chiefly to pH and not to the specific chemical. Our feeling has been that stone dissolution problems should be studied as specifically as possible and that no one solution should be tried as a catch-all for any type of stone. This is especially important in the laboratory when the basic facts are being studied. Our clinical experience with "Sequestrine" is very limited. We have used this solution in only two patients and both of these complained of so much pain that a fair test was not completed.

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* The paper by Dr. Gehres will be published in the March issue. *Editor*

Dr. Linwood D. Keyser (Roanoke, Va.): Gentlemen, this could well be a landmark in the treatment of urinary stone. That two observers, Dr. Gehres and Dr. Abeshouse associated with Dr. Weinberg, working independently far apart in different clinics should report almost identical experiences with a new stone solvent, is most remarkable.

These initial reports are promising. However clinical experience and comparison with other stone solvents over a period of time will be necessary to fully evaluate the use of this drug.

In looking for the ideal solvent for use in retrograde dissolution of calculi several factors must be considered First, the solvent should be active within a few days showing a definite diminution in the size of the stone by x-ray. The tolerance of the individual patient to indwelling catheters and to lying in bed running an irrigator over days and weeks is variable. At best it constitutes a severe economic, physical and psychologic strain.

Second, the solvent should attack dense as well as less compact stones. It is the feeling of myself and chemists working with me on this problem that the degree to which crystals are cemented together by the organic framework of the calculus is of prime importance in their dissolution. For the most part the stones which we have dissolved in the past are soft, recently formed calculi. Denser hard concrements are more resistant. We are under the impression that stones of recumbency undergo disintegration or yield to dissolution methods more easily because they are largely composed of inspissated crystals with little organic matter in them.

Third, the ideal retrograde stone solvent must be well tolerated and have a minimal irritating effect upon the renal parenchyma. Continuous irrigation with any solution, even isotonic saline, may after a time produce an exacerbation of pyelonephritis. With acid or irritating solutions this may become highly dangerous.

Again we must continue the search for stone solvents which may be given by mouth and produce a solvent reagent in the urine, an ideal which we may conceive of as possible if we have a kidney with reasonably good function. The achievement of dissolution of certain soft alkaline stones with acidifying drugs and diets and vitamines; Greta Hammarsten's dissolution of experimental oxalate calculi in rats by a diet rich in magnesium, calcium and vitamines; the use of hippuric acid by Snapper, Bendein and Pollak; Schorr's attack with low calcium phosphorus dietary combined with amphogel and estrogens; all these efforts are well known. While they have not answered the problem, they do stimulate us as to further investigation of this approach.

At Virginia Polytechnic Institute Dr. Claffey and associated chemists have continued to collaborate with me in the study of the composition of calculi and their response to solvents. Hylonuronidase with G solution has been tried with partial success but its clinical use has not been effective as a solvent in the few cases in which it has been tried. Recently we have found that 0.1 per cent potassium permanganate in an acetic acid sodium acetate buffer at pH 4 is highly effective in dissolving most stones, even oxalates, in the irrigator. I have not tried this clinically because it is probably too irritating. Besides the deposition of manganese dioxide in the tissues would be objectionable.

We are convinced that we must know more of the nature of organic matter in calculi. We are at present concerned with the separation of this organic matter from dissolved stones by electrodialysis against various dialyzing solutions such as pure water, G solution and dilute hydrochloric acid. In a series of stones thus far studied we find the content in organic matter is extremely variable, as is the response of this extracted organic matter to urease and other ferments. We are hopeful that continued study will help us to learn more of the chemical nature of the organic material in stones and in turn to find some means of causing its disentegration.

Finally I wish again to congratulate Dr. Abeshouse and Weinberg and Dr. Gehres for their remarkable presentations. I am certain that we shall all look forward to a clinical trial of the solvent which they have given us.

DR. BENJAMIN S. ABESHOUSE (Baltimore, Md.): We have been trying a whole series of new chelating agents from various factories that have been kind enough to send them to us. Some work almost as well as versene. We have even gotten in touch with some organic chemists who are modifying this versene with various radicals and we think, though we are not sure, that we might be able to give it by mouth.

I have been asked, how did I get into this business of stone solvents. Let me tell you how I did because I think it is an amusing story. When I got back from Los Angeles last year, I was rather tired. I went out on the porch and sat down, and my neighbor, a manufacturing chemist, came over and wanted me to go out and play golf. I said, "I am too tired," so we sat there and talked. We finally got around to the problems he had, and he told me that he had just manufactured 20 barrels of green soap for commercial use and it all came back because it was impure. At least it looked impure as it had had a fine precipitate which was filtered out and found to contain sodium carbonate, calcium phosphate, calcium oxalate, and a little calcium chloride. The problem was how to get these salts out of the soap solution. He found out through the American Chemical Society that there was a chelating agent called versene that was used to clean out boilers, and also to soften water. He bought about 10 pounds of it. It cost him about $6, and thus he cleaned up $20,000 worth of soap.

I said, "Can I get some of that?" and he said, "Sure," and the following morning at eight-thirty, I went down to his plant and was given a pound. I went back to the laboratory and told the laboratory assistant to make up various solutions, i.e., 1 to 50 per cent, and put it in test tubes with stones of definite composition. I came back 6 hours later and found that most of the stones were dissolved, and so we knew we had something "hot." Then we went on which the rest of the study.

I do want to thank Dr. Keyser for his gracious and kind discussion, and I again want to tell you that I think Dr. Gehres deserves the credit for a fine piece of work.

Dr. Robert F. Gehres (Sacramento, Calif.): I wish to thank Dr. Abeshouse for his very generous remarks about our efforts, and Dr. Keyser for his constructive comments concerning the work. The words of both these men mean a great deal to us; Dr. Abeshouse because of his contribution to urology in general, and Dr. Keyser for what he has done to increase our knowledge of the cause, treatment and prevention of urinary calculus disease. His pioneering efforts in the developments and use of stone solvents have guided us in this work.

It is important to impress upon you the fact that the solution is apparently effective against all types of urinary calculi containing calcium, even though it be only a trace, and that it takes but a relatively short time for it to do its work. Many various sized, hard stones have been dissolved in only a few hours by contact with the solution in vitro, and others have been dissolved within two or three days by intermittent irrigation in vivo at infrequent intervals. After perfection of technique, the latter was well demonstrated in the last 2 patients treated at the Squier Clinic. Again I wish to say that no toxic effects were noted in any patient treated, except in the one in which the solution was of an exceedingly high pH and contained lithium.

We wish to express our appreciation and gratitude to Dr. B. C. Seegal, executive officer of the department of bacteriology of the College of Physicians and Surgeons of Columbia University, for her kind interest in providing facilities and giving direction to this work, and to Dr. George F. Cahill, director of the J. Bentley Squier Urological Clinic of the Columbia Presbyterian Medical Center, for his encouragement and financial support which made this study possible.

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CLINICAL EXPERIENCE WITH TERRAMYCIN IN TREATMENT OF REFRACTORY URINARY TRACT INFECTIONS

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Terramycin, a new anti-microbial agent derived from a soil actionmycete, has a wide anti-bacterial spectrum embracing both gram positive and gram negative organisms. The material possesses a low degree of toxicity, both acute and chronic, in experimental animals. Terramycin is an amphoteric substance which is sparingly soluble at neutrality, while its sodium salt and the hydrochloride are each freely soluble. On the basis of animal studies, the hydrochloride was selected as the preparation of choice for oral administration in clinical work. This preliminary report deals with the results of therapy in a group of patients with long standing urinary tract infections which had not been successfully controlled by various other therapeutic agents.

MATERIAL AND METHODS

Terramycin hydrochloride,* a light yellow powder, was administered in capsules, each of which contained the equivalent, in biologic activity, of 250 mg. of pure terramycin base. Relatively large oral doses were deliberately employed since an evaluation of possible toxicity was one of the objectives of this study. An initial loading dose of 2.0 gm. was followed by 1.0 or 1.5 gm. at 6 hour intervals. The duration of therapy varied considerably, but was usually continued for a minimum of 1 week, except in three instances where the patients experienced moderately severe nausea and vomiting, and refused further medication.

The patients who were studied had infectious processes at various localities in the urinary tract. All had disease of long standing, and in many of them there had been a variety of infecting organisms at different periods during the course of the illness. The drug was not used in any case where major obstructive uropathy, calculous disease, or neoplasm was present. However, objective evidences of chronic inflammatory disease were found in the majority of the cases, either in the bladder by cystoscopy, or in the kidneys by pyelography. It was believed that this type of case would constitute a formidable test of the therapeutic value of terramycin.

Aerobic cultures of the urine were obtained within 24 hours prior to starting therapy, during treatment, and at intervals up to 1 month after discontinuing the drug. The sensitivity of bacteria isolated from patients during these periods was determined by a simple technique utilizing a series of dilutions of terramycin. The lowest dilution giving complete inhibition of growth at 24 hours was con-

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Read at annual meeting. American Urological Association, Washington, D. C., June 1, 1950.

* Supplied through the courtesy of Dr. Gladys Hobby of the Charles Pfizer Co., Inc., Brooklyn, N. Y.

sidered to be the sensitivity of the strain under study. Concentrations of terramycin in serum and in urine were measured by a tube dilution method similar to that employed for penicillin assay utilizing the hemolytic streptococcus C 203 MV as a test organism.

White blood cell counts, hemoglobin determinations, and urine examinations were made daily throughout the period of treatment. Bromosulfalein tests of liver function were done before and within 48 hours of cessation of therapy. Frequent determinations of the blood nonprotein nitrogen were made throughout the period of observation in all patients, and in 10 patients serial urea clearances were done covering the period of therapy.

RESULTS OF THERAPY

Table 1 gives the pertinent data on the 24 patients included in this report. Analysis of these data reveal that 20 of the 24 patients treated had initial satisfactory response to therapy with disappearance of the bacteria originally identified by culture. In most instances this effect was a prompt one occurring within 48 hours after the institution of treatment, and was associated with resolution of, or marked diminution in pyuria. Ten of these cases remained free of their initial pathogens for a minimum follow-up period of 2 weeks, but of these, 4 subsequently developed re-infection with a different organism. Thus only 6 of the 24 were actually controlled in the limited period covered by this study. Of the 14 cases considered as failures, 10 had negative cultures during therapy only to have recurrence of the infection with the same bacteria within 1 week of the conclusion of treatment, and 4 cases proved totally refractory to therapy.

On the doseage schedule used, the concentration of terramycin in serum ranged from 1.65 to 16.5 micrograms per cubic centimeter. Those who had known reduction in renal function were found to have serum levels in the higher limits of this range in most instances. Urine levels of from 200 to 1000 micrograms per cubic centimeter were observed.

There was no consistent correlation between the levels of terramycin in the serum, the sensitivity of the organism, and the outcome of treatment, although the organisms showing the highest in vitro resistance were least influenced by therapy. A detailed account of the development of resistance to terramycin in the organisms from these and other patients will be published elsewhere. There were, however, several instances in which the strains obtained after completion of therapy showed a significant increase in resistance when compared with those isolated prior to treatment.

TOXICITY

Blood cell counts and bromsulfalein tests of liver function gave no evidence of toxic effect on the hematopoietic system or on the liver. Seven of the 24 patients had transitory elevations of the nonprotein nitrogen during treatment which returned to normal or pre-therapy levels within 48 hours after conclusion of therapy. In many of these the return to normal levels began while the terramycin was still being administered. Since there were no alterations in the urinalysis of

TABLE 1. *Data on 24 patients with chronic urinary tract infections treated with terramycin.*

NUMBER	PATHOLOGIC DIAGNOSIS	BACTERIOLOGIC DIAGNOSIS	SENSITIVITY TO TERRAMYCIN IN MICROGRAMS/CC	PREVIOUS THERAPY	TOTAL DOSE OF TERRAMYCIN	DAYS OF THERAPY	TERRAMYCIN* CONCENTRATION MICROGRAMS/CC	CULTURE DURING THERAPY	FOLLOW-UP CULTURE	RESULTS	REMARKS ON TOLERANCE
					gms.						
1	Chronic pyelonephritis	Streptococcus fecalis	0.5 cc	Sulfonamides Penicillin Streptomycin Chloromycetin	26	6	S—5.0–10.0 U—500–2500	Negative in 24 hours and thereafter	Negative two weeks post-therapy	Good	Nausea, loose stools & occ. vomiting
2	Chronic pyelonephritis	Escherichia coli	1.0 cc-	Sulfonamides Penicillin Streptomycin Chloromycetin Aureomycin	40	11	S—3.3–5.0 U—500	Negative in 24 hours & thereafter	Negative four weeks post-therapy	Good	Nausea, loose stools & occ. vomiting
3	Chronic pyelonephritis	Streptococcus fecalis	0.5 cc	Aureomycin Chloromycetin	42	10	S—2.5–16.5 U—1000	Strep. fecalis negative in 4 days, B. alkaligenes persisted	Died 7 days post-therapy	Failure	No symptoms of intolerance
		Bacillus alkaligenes	2.5 cc								
4	Chronic purulent cystitis	A. aerogenes	0.5 cc	Sulfonamides Penicillin Streptomycin	44	7	S—4.9–12.5 U—1000	Negative in 36 hours and thereafter	Strep. fecalis appeared 6 days post-therapy	Temporary benefit re-infection	Loose stools
5	Chronic purulent cystitis	Pseudomonas aeruginosa	5.0 cc	Sulfonamides Streptomycin Chloromycetin Polymyxin	62	13	S—1.65–12.5 U—200	Negative in 36 hours & thereafter	Negative 4 weeks post-therapy	Good	Nausea, severe diarrhea
6	Chronic pyelonephritis	Pseudomonas aeruginosa	2.5 cc	Sulfonamides Aureomycin Chloromycetin	7	1	— —	Negative in 24 hours	Reappeared 4 days post-therapy	Failure	Refused therapy after 24 hours because of nausea & vomiting
7	Chronic pyelonephritis	Pseudomonas aeruginosa	15.0 cc	Sulfonamides Penicillin Streptomycin	9	1½	— —	Remained positive	Remained positive	Failure	Refused therapy after 24 hours because of nausea & vomiting

8	Chronic cystitis Acute pyelonephritis	Aerobacter aerogenes	2.5 cc	Sulfonamides Penicillin	34	8	S—4.9 U—500	Negative in 24 hours & thereafter	Strep. fecalis appeared 2 wks. post-therapy	Temporary benefit re-infection	No symptoms of intolerance
9	Alkaline encrusting cystitis	Aerobacter aerogenes	—	Sulfonamides Pencillin	30	7	S—7.5 U—26.4	Negative in 4 days	Strep. fecalis appeared 15 days post-therapy	Temporary benefit re-infection	No symptoms of intolerance
10	Chronic cystitis	Aerobacter aerogenes	1.0 cc	Penicillin Sulfonamides Streptomycin	34	8	S—4.9-7.5 U—1000	Negative in 24 hours	Reappeared in one week	Temporary improvement	No symptoms of intolerance
11	Chronic pyelonephritis	Pseudomonas aeruginosa	2.5-5.0 cc (two strains)	Sulfonamides Streptomycin Aureomycin Chloromycetin Polymyxin	46	11	S—7.5 U—400	Negative in 24 hours	Reappeared during therapy	Temporary improvement	No symptoms of intolerance
12	Chronic cystitis	Aerobacter aerogenes	1.0 cc	Sulfonamides Penicillin Streptomycin	38	9	S—1.5-7.5 U—300	Negative in 24 hours	Reappeared 10 days post therapy with E. freudii as well	Temporary improvement	No symptoms of intolerance
13	Chronic cystitis	Aerobacter aerogenes Streptococcus fecalis	0.5 cc 0.5 cc	Sulfonamides Penicillin	20	6	S—4.9-7.5 U—750	Negative in 24 hours	Reappeared on 4th days of therapy & persisted	Temporary improvement	No symptoms of intolerance
14	Acute pyelonephritis	Aerobacter aerogenes Streptococcus fecalis	0.5 cc 0.5 cc	none	34	8	S—3.0-4.9 U—300	Negative in 24 hours	E. coli & Strep. fecalis reappeared on 10th post-therapy day	Temporary benefit re-infection	Loose stools
15	Chronic pyelonephritis	Escherichia coli	15.0 cc	Sulfonamides Streptomycin Chloromycetin Aureomycin	42	10	— —	Negative in 24 hours & thereafter	Negative 4 weeks post-therapy	Good	Nausea & anorexia
16	Chronic pyelonephritis	Escherichia freundii	0.5 cc	Sulfonamides Streptomycin Chloromycetin	20	6	S—7.5 U—600	Negative in 48 hours	Negative three weeks post-therapy	Good	Refused drug on 6th day due to nausea & vomiting
17	Chronic cystitis	Pseudomonas aeruginosa Aerobacter aerogenes Streptococcus fecalis	5.0 cc 50.0 cc 15.0 cc	Sulfonamides Streptomycin Chloromycetin	20	7	S—7.5 U—500	Ps. aeruginosa negative in 60 hours Strep. fecalis negative in 84 hours A. aerogenes persisted	Streptococcus fecalis only organism isolated 4 weeks post-therapy	Failure	Nausea & anorexia

TABLE 1—*Concluded*

NUMBER	PATHOLOGIC DIAGNOSIS	BACTERIOLOGIC DIAGNOSIS	SENSITIVITY TO TERRAMYCIN IN MICROGRAMS/CC	PREVIOUS THERAPY	TOTAL DOSE OF TERRAMYCIN	DAYS OF THERAPY	TERRAMYCIN* CONCENTRATION MICROGRAMS/CC	CULTURE DURING THERAPY	FOLLOW-UP CULTURE	RESULTS	REMARKS ON TOLERANCE
					gms.						
18	Chronic cystitis	Pseudomonas aeruginosa Aerobacter aerogenes	2.5 cc 1.0 cc	Sulfonamides Penicillin Streptomycin	38	9	S—3.75 U—500	Ps. aeruginosa negative by 8th day Aerobacter negative in 24 hrs.	Ps. aeruginosa returned in 2 weeks with Strep. fecalis in addition. Aerobacter negative	Failure	No symptoms of intolerance
19	Chronic cystitis	Escherichia coli Aerobacter aerogenes Streptococcus fecalis	1.0 cc 2.5 cc —	Sulfonamides Penicillin Streptomycin	28	7	S—10.0 U—300	Negative in 48 hours	A. aeroges & Strep. fecalis reappeared one week post-therapy. E. coli negative	Temporary improvement	No symptoms of intolerance
20	Chronic pyelonephritis	A. aerogenes	1.0 cc	Penicillin	16	8	S—10.0 U—200	Negative in 72 hours	A. aerogenes reappeared one week post-therapy with Strep. fecalis	Temporary improvement	No symptoms of intolerance
21	Chronic cystitis	Streptococcus fecalis	2.5 cc	Sulfonamides Penicillin Aureomycin	33	8	S—4.0 U—250	Negative in 48 hours	Strep. fecalis reappeared on 7th post-therapy day	Temporary improvement	No symptoms of intolerance
22	Chronic cystitis	Staphylococcus aureus	0.5 cc	Sulfonamides Penicillin Chloromycetin	22	7	S— U—200	Negative in 24 hours	Negative one week post-therapy	Good	No symptoms of intolerance
23	Chronic cystitis	Pseudomonas aeruginosa	2.5 cc	Sulfonamides Penicillin Chloromycetin	28	7	— —	Negative in 24 hours	Negative one week post-therapy	Good	No symptoms of intolerance
24	Chronic pyelonephritis	Paracolon	50.0 cc	Sulfonamides Penicillin Chloromycetin	20	7	S—5.0 U—200	Remained positive	Remained positive	Failure	Nausea & anorexia

* S = serum
U = urine

these patients indicative of renal damage, and since these elevations of nonprotein nitrogen occurred in many of the patients who evidenced considerable nausea and vomiting, it is probable that such changes as were noted were due to dehydration. In that terramycin is a very acid drug, and in that the urinary pH of all patients under treatment was uniformily reduced to a range of 4.5 to 5.0, it is conceivable that this factor as well contributed to the dehydration. In the ten patients followed by serial estimations of renal function with urea clearance tests there was no evidence of significant departure from normal or pre-therapy determinations.

Anorexia or mild nausea was not uncommon, but actual vomiting was rare and was confined to women. In two female patients given large initial dosage (3.0 gm.) vomiting was prominent and further medication was refused after 24 hours of treatment. Significantly, both of these patients had vomited all previous medication. Loose, bulky stools were frequently noted, and in 1 case there was severe diarrhea. Nausea and vomiting were usually controlled by the concomitant administration of food with the drug, and the diarrhea managed with paregoric. Dermatitis venenata occurred on the sixth day of treatment in one patient who had had similar difficulties with other chemotherapeutic and antibiotic agents.

DISCUSSION

The patients used in this study were all possessed of chronic infectious processes involving the urinary tract against which a wide variety of antimicrobial agents had been noticeably ineffectual. It is a well known fact that devitalized tissue, or tissue involved by chronic inflammation offers an effective mechanical barrier to healing. Under such circumstances the use of a drug which is principally bacteriostatic allows for the survival of residual organisms, and these provide the nidus for subsequent relapse. It has been the clinical impression of most physicians responsible for the management of such cases that many patients who harbor urinary tract infections, in which the predominant clinical characteristic is that of chronicity, remain refractory to therapy even though bacteriologic in vitro sensitivity studies would seem to predict a satisfactory therapeutic response. In the present study there were several instances in which the one or more organisms which were identified by pre-treatment culture disappeared during therapy only to be replaced by bacteria not previously recognized. In each instance these late appearing bacteria were relatively resistant to terramycin. It is doubtful that this represents a new infection. More likely, the suppression of the overshadowing primary offenders allowed proliferation in these devitalized tissues of organisms which were already present in small numbers and possessed of native resistance to the drug. Such a sequence of events has been frequently noted with the use of other chemotherapeutic preparations.

While this series is admittedly small, and the types of bacteria represented limited, it is the impression of the authors that terramycin is as good as, and may in the future prove superior to, other available chemotherapeutic and antibiotic agents in some types of infection. It was rather surprising to find such a satisfactory response in infections due to Pseudomonas aerugunosa, an organism notoriously insensitive to most drugs used in the therapy of urinary tract infections. Therapeutic control was effected in three patients with this organism and temporary complete suppression in three others. It is significant that two of these cases had previously proven completely refractory to polymyxin.

The experience here reported certainly indicates that terramycin is a relatively nontoxic agent, and that it has a marked suppressive action against infections due to organisms sensitive in vitro to its action. It is anticipated that further investigation will prove it to be a very useful adjunct to the drugs presently available for the control, not only of chronic refractory processes, but in a high percentage of acute infections as well.

SUMMARY AND CONCLUSIONS

Terramycin was used in the treatment of 24 cases of chronic urinary tract infections refractory to all previous attempts at therapy.

In 10 cases the initial infection was controlled, but in 4 of these re-infection with a new organism occurred.

Fourteen of the cases did not respond. Ten of these obtained prompt and satisfactory temporary improvement while under medication but relapsed on withdrawal of the drug, while 4 were refractory from the start.

This agent has demonstrated its value as an addition to the armamentarium of the physician treating urinary infections, because it will cure some where all other anti-bacterials have failed. The extent of its usefulness in handling acute infections must yet be determined.

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DISCUSSION

DR. GRAYSON CARROLL (St. Louis, Mo.): This report on terramycin is thorough and informative. Our studies, also, indicate that it is a safe drug and a valuable addition to our expanding number of antibiotics. As indicated by the essayists, it has inhibited organisms which were resistant to all other known drugs. A high percentage of our patients complained of diarrhea. A small percentage complained of nausea. See table 1. The drug failed to inhibit any of our strains of Proteus. The drug was found most effective in Escherichia coli, Aerobacter aerogenes, Alcaligenes, Streptococcus fecalis and Staphylococcus aureus. Sixty per cent of the strains of Pseudomonas were inhibited some of which were uninhibited by all other antibiotics.

Of 33 patients treated with terramycin, only 5 remained unaffected. Table 2 gives the detail of this study.

Table 3 gives the result of the study of 105 organisms tested in vitro. Our report appears more favorable than that of the essayists. We used different criteria. We considered that a result was favorable when the urine became clear and the culture was negative after the drug had been discontinued. If the same organism or a different organism appeared later in the patient, we considered that it was not a failure of the drug but a failure of the antibiotic to come in contact with the organism, due to poor drainage, microscopic abscess formation or scar tissue with poor blood supply. We believe that recurrence emphasizes the limitation of an antibiotic. It is at best an auxiliary to sound diagnosis and surgical relief.

We believe, also, that there is a direct relationship of the in vitro findings and the clinical result. We explain a clinical failure, not by ineffectiveness of the antibiotic but due to the nature of the lesion or the condition of the host, recognizing that even granulation tissue can hide organisms in such a manner as to prevent them from being exposed to the administered antibiotic.

We have endeavored to set up a spectrum so that clinically, when an organism is identified by culture, the clinician can select the drug that is most likely to inhibit that organism. Table 4 represents the result of this endeavor.

DR. R. FRANK JONES (Washington, D. C.): Terramycin was made available to the staff of Freedmen's Hospital for evaluation in a large group of diseases. A report of the early results appeared in the J. A. M. A. for May 10, 1950. Its use has been continued by the Division of Urology, and the findings of its effect in 20 cases of chronic urinary infections are reported to you.

These patients had been under our care from several weeks to nearly ten years, during which time they had been treated by the antibacterial measure which was known to be the most effective in destroying the causative organism. Only 4 of the 20 cases had had a single antibacterial measure applied, while the remaining 16 had been treated with many combinations of penicillin, sulfonamides, streptomycin, aureomycin, mandelic acid and urotropin.

Urine cultures and pus cell counts were made at the beginnng of therapy.

TABLE 1. *Toxic effects of terramycin*
No serious toxic effects

SYMPTOMS	NO. OF PATIENTS
*Diarrhea	10
Nausea	6
Vomiting	2
Sore mouth	1
Esophogeal burning	2

* 5 patients: severe diarrhea post-treatment.

TABLE 2. *Terramycin in vivo*

ORGANISM	SENSITIVITY IN MICROGRAMS/MILLILITER						RESULTS
	0.01	0.04	0.17	0.7	2.8	11.4	
Escherichia coli		1	8				9 Controlled
Escherichia intermediate	1		3				4 Controlled
Aerobacter aerogenes		2	2	2			6 Controlled
Paracolon coliforme		1					1 Controlled
Proteus vulgaris					3	1	4 Failures
Pseudomonas aeruginosa		1	1	1	2	1	5 Controlled 1 Failure
Alcaligenes fecalis							—
Streptococcus fecalis	1					1	2 Controlled
Staphylococcus albus	1						1 Controlled
Dosage: 2 capsules (250 mg.) every 6 hrs. for 3 days							28 Controlled 5 Failures

TABLE 3. *Terramycin sensitivities of 105 organisms*
Mcg./cc

	NO.	0.01	0.04	0.17	0.7	2.8	11.4	>11.4	% SENSITIVE
Escherichia coli	35		8	26	1				100
Escherichia intermediate	11	2	1	6	1		1		91
Aerobacter aerogenes	13		2	5	4	1	1		85
Paracolon coliforme	1	1							100
Proteus vulgaris	12				2	6	3	1	17
Pseudomonas aeruginosa	15		1	1	7	3	2	1	60
Alcaligenes fecalis	5			4	2				100
Streptococcus *fecalis*	7	4	3						100
B. hemolytic streptococcus	1						1		—
Staphylococcus aureus	4	3		1					100
Staphylococcus albus, B. hemolytic	1						1		—

The clinical symptoms were evaluated. The infecting organisms were in pure culture in 16 and mixed in 4. The pus cells per high power field uncentrifugalized ranged from a few to innumerable. Frequency, dysuria and urgency were the most common symptoms. Sixteen patients were postoperative; 11 from prostatectomies, suprapubic, retropubic and perineal; 2 following removal of kidney stones; 1 each from stones in the ureter and bladder; and 1 from cystectomy with bilateral ureteral transplantation to the skin.

It was decided to give a standard dose of 10 gm. terramycin over 5 days at 6 hour intervals. The urine was studied microscopically for pus cells and cultured for organisms during each day of therapy.

The clinical results of this study were satisfactory for every patient was benefited within the 5 days of therapy.

There was elimination of all symptoms in most of the patients.

There was reduction of the pyuria and bacteriuria in all and complete eradication of organisms in many.

TABLE 4. *Antibiotics and chemotherapeutic agents with their practical application in urinary infections*

ORGANISM	DRUG SHOWING % INHIBITION						CHOICE OF DRUG IN ORDER OF EFFICACY
	Penicillin	Strepto-mycin	Aureo-mycin	Chloromy-cetin	Gantrisin	Terra-mycin	
Escherichia coli	Resistant	84	88	96	87	100	Terra—Chloro—Aureo
Escherichia intermediate	Resistant	33	96	73	27	91	Aureo—Terra—Chloro
Aerobacter aerogenes	Resistant	44	94	39	0	85	Aureo—Terra—Strep
Paracolon	Resistant	50	83	55	62	100	Terra—Aureo—Gant
Proteus	Resistant	77	13	83	70	17	Chloro—Strep—Gant
Pseudononas	Resistant	5	14	0	0	60	Terra—Aureo—Strep
Alcaligenes	Resistant	30	80	33	0	100	Terra—Aureo—Strep
Streptococcus fecalis	Resistant	0	100	100	0	100	Chloro—Aureo—Terra
S. hemolyticus	Resistant 95 plus	—	—	—	—	—	Pen—Terra
S. aureus	95 plus	—	—	—	—	100	Terra—Pen
Desired ph of urine	Acid	Alk.	Acid	Acid	Either	Acid	

There was permanent elimination of many organisms, and change of bacterial flora in many cases.

The most susceptible organisms bacteriologically were the Pyocyaneus, B. mucosus capsulatus and paracolon. The A. aerogenes and E. coli were next in susceptibility, whereas the Staph. albus, Staph. aureus and Strep. fecalis were most resistant. The Proteus was resistant in every case.

Benefit seemed not to be related to the urinary pH.

Clinical improvement was noted in every case by subsidence of symptoms and sharp decline in the pus cell count. There was sometimes culture reversal, notwithstanding the presence of stones in the kidney and bladder and stricture of the urethra.

There were no toxic reactions though there were some side reactions. One patient persistently regurgitated the drug immediately upon swallowing it.

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SKF 538-A:* A NEW TOPICAL ANESTHETIC FOR USE IN THE URETHRA: A PRELIMINARY REPORT

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Approximately one year ago we received for clinical trial as a topical anesthetic a new compound, SKF 538-A, or 1-(beta-dimethylaminoethoxy)-3-Butylisoquinoline monohydrochloride. Pharmacological studies[1] in the manufacturer's laboratories had indicated that this drug might compare favorably with nupercaine hydrochloride (hereinafter called nupercaine) which is known as the most potent but also the most toxic of the commonly used local anesthetics.[2] Their findings are summarized in table 1. According to these tests, the new compound has an anesthetic effect about 10 times that of nupercaine, an 0.001 per cent concentration of SKF 538-A and 0.01 per cent solution of nupercaine giving comparable anesthesia of the rabbit eye. They emphasized, however, that the rabbit eye is a very sensitive test medium and that such results could hardly be expected to show up in ordinary clinical use. Moreover, its toxicity for the laboratory animal is less than that of nupercaine, although greater than that of procaine or cocaine. Thus, solutions of SKF 538-A that are equipotent with nupercaine should fall in the toxicity range of procaine. Subacute toxicity studies conducted for 30 days on rats and guinea pigs revealed no pathological changes attributable to the compound. Patch test studies on abraded, as well as intact skin showed SKF 538-A to be free of primary irritant or allergenic action. Surface tension studies revealed that 0.25 per cent SKF 538-A solution had a surface tension of 40.5 dynes/cm. when tested by the DuNouy Tensiometer-Ring method at 25C (surface tension of water being 72.0 dynes/cm.) In comparative tests, a solution of nupercaine hydrochloride (0.17 per cent) made by dissolving one tablet in 30 cc of distilled water, had a surface tension of 60.0 dynes/cm. at 25 C.

This anesthetic has now been used in 403 patients for urologic instrumentation. The procedures included urethral dilatation with sounds, cystoscopic examination of the bladder, topical application of 20 per cent silver nitrate to the urethra and trigone in the female, hydraulic dilatation of the bladder for interstitial cystitis, and a few instances of instrumental dilatation of the ureter. From 181 patients who had undergone similar instrumentation previously with topical nupercaine anesthesia it was possible to obtain an impression of the comparative effectiveness of the two anesthetics.

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* SKF-538-A solutions used in our study were provided by Smith, Kline & French Laboratories, Philadelphia, Pa.

[1] Fellows, E. J. and Macko, E.: Local Anesthetic Activity of a Series of Aminoalkoxy Isoquinolines. Presented at annual meeting of the American Federation Societies meeting, Detroit, Mich., April 18–22, 1949.

[2] Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics. New York: the Macmillan Company, 1941, p. 302.

METHOD

SKF 538-A was administered in essentially the same manner as that which has been employed with nupercaine 0.17 per cent for a number of years. In the male, 30 cc of the solution is injected slowly through the urethra with a bulb syringe and contact with the urethral mucosa is maintained for 5 minutes by applying a clamp to the end of the penis. In the female, 30 cc of the anesthetic is injected from a bulb syringe through the urethral meatus. Slow injection of the drug is believed to be important. After injection is stopped, solutions remain in effective contact with the mucosa over the internal and external sphincters for only a few seconds; this can be demonstrated in serial x-rays during and following injection of a nonviscous radiopaque medium. These two segments of the urethra are most sensitive and are subjected to the greatest degree of pressure by the rigid shaft of a straight urethral instrument. Thus the slower the rate of injection of the anesthetic the more prolonged is its contact with these two important segments of the urethra.

TABLE 1

COMPOUND	LOCAL ANESTHETIC ACTIVITY AFTER TOPICAL APPLICATION TO RABBIT'S EYES		ACUTE TOXICITY AFTER INTRAPERITONEAL INJECTION IN RATS
	Concentration %	Duration of Anesthesia (Min.)	Approx. LD-$_{50}$ (mg./kg.)
Procaine	1.0	2 (?)	225 mg./kg.
Cocaine	1.0	18	75–100 mg./kg.
Nupercaine	0.01	69.2	30 mg./kg.
	0.001	none	
SKF No. 538-A	0.1	514 (8 hrs. 34 min.)	
	0.01	199 (3 hrs. 19 min.)	45–50 mg./kg.
	0.001	75	

SKF 538-A was used in concentrations ranging from 0.05 per cent to 0.30 per cent, with the object of determining which strength might be most practical for clinical use.

EVALUATION OF RESULTS

The interpretation of the results of a study of this type is admittedly most difficult. The only basis for comparison of the degree of anesthesia produced by different topical anesthetics is a subjective one which is dependent upon the patient's evaluation of his own discomfort. When there has been no previous instrumentation for comparison, evaluation of the degree of anesthesia is even more difficult and must depend primarily upon the judgment and experience of the operator. Every effort was made to interpret the results as objectively as possible in this study.

In grading the degree of anesthesia produced by SKF 538-A, as compared to that of previous nupercaine anesthesias for similar instrumentations, the results were arbitrarily divided into four groups: No. 1, the same amount, or more pain than with previous nupercaine; No. 2, less pain, No. 3, much less pain, and No.

4, no pain (a feeling of pressure only). In evaluating the degree of anesthesia in patients who had no previous instrumentation to serve as a basis for comparison, the results were classified into three groups: No. 1, poor to fair anesthesia; No. 2, good anesthesia; No. 3, complete anesthesia.

DISCUSSION OF RESULTS

The results are summarized in tables 2 and 3.

Of the 181 patients previously treated with topical nupercaine for similar instrumentations, 84.5 per cent reported less discomfort with SKF 538-A (table 2). In the remaining 222 patients who had undergone instrumentation previously without local anesthesia or with an unknown anesthetic, or had had no previous instrumentation at all, there was good to complete anesthesia in 78.8 per cent (table 3). Altogether, little or no pain was reported by a total of 298 of the 403 patients, or 74.3 per cent.

TABLE 2. *Effectiveness of SKF 538-A as compared with nupercaine 0.17 per cent*

CONC. SKF 538-A PER CENT	TOTAL PATIENTS	NO DIFFERENCE	A. LESS PAIN	B. MUCH LESS PAIN	C. NO PAIN	TOTAL: LITTLE OR NO PAIN (B & C) %
0.05	9	5	2	2	0	22.2
0.10	75	15	22	33	5	50.7
0.15	45	6	4	16	19	77.7
0.25	43	2	2	11	28	90.6
0.30	9	0	0	0	9	100.0
Total................	181		84.5%			

TABLE 3. *Estimated effectiveness of SKF 538-A, no comparison with other anesthetics*

CONC. SKF 538-A	TOTAL PATIENTS	A. POOR TO FAIR ANESTHESIA	B. GOOD ANESTHESIA	C. COMPLETE ANESTHESIA	% GOOD TO COMPLETE ANESTHESIA (B & C)
0.1%	52	16	30	6	69.2
0.15%	64	14	20	30	78.1
0.25%	69	9	31	29	86.9
0.3%	37	8	10	19	70.3
Total................	222				

We believe that it is significant that 145 patients, 36 per cent of the total, experienced no pain, feeling only some pressure from the passage of the instrument, and of these only 6 were female. It is apparent from the tables that increasingly higher concentrations of SKF 538-A provided greater protection. This was confirmed in 26 cases treated with different solutions of SKF 538-A for two or more instrumentations; all except one noted a greater degree of anesthesia when a higher concentration was used. Of the patients receiving 0.15 per cent or higher concentrations of SKF 538-A, 134 or 57 per cent experienced no pain at all. On a basis of the results depicted in tables 2 and 3, 0.25 per cent SKF 538-A was selected as the optimum concentration for clinical use.

In 3 patients with ureteral stricture 15 cc of the anesthetic solution was gently instilled into the renal pelvis and ureter through a small catheter prior to instrumental dilatation. All noted considerably less pain on the passage of a larger dilating bougie than with the initial small catheter.

Hydraulic dilatation of the bladder for interstitial cystitis was carried out after instillation of SKF 538-A in a small number of paitents. The results were inconclusive, some experiencing as much or more discomfort than on previous dilatations and others, less discomfort. In 2 patients, however, the capacity of the bladder on forced distention was doubled following instillation of the anesthetic solution.

Prompt relief of bladder spasm, occurring during cystoscopy, was obtained in a few patients following injection of 30 cc of SKF-A-538 through the cystoscope sheath.

REACTIONS

Four patients in this series developed urethral bleeding immediately following injection of the anesthetic solution. In one, the bleeding was rather profuse and lasted several hours. In the other three, it was slight. This incidence of bleeding is no higher in our experience than when nupercaine is used and is thought to be mechanical in nature, a result of overdistention of the urethra. One patient who had been cystoscoped many times previously with nupercaine anesthesia stated that he felt faint following the first instillation of 0.25 per cent SKF 538-A, but this was transient and no other systemic effects were noted. Occasionally, slight burning in the urethra was noted for a few seconds after injection. This occurred most frequently in the group receiving the 0.3 per cent solution. Two other complications occurred, but they cannot be attributed to the anesthetic. In 1 case, a Negro with a dense urethral stricture, the instillation was made too energetically, resulting in extravasation of both anesthetic and air into the subcutaneous tissues of the penis. Vigorous antibiotic treatment was immediately instituted and the extravasation subsided without ill effect. In another patient, rather marked edema and swelling of the soft tissues of the penis followed cystoscopy under local SKF 538-A. Subsequent skin testing by patch test revealed that the individual was sensitive to cystan, the antiseptic solution in which the cystoscopes were kept, and the patch test for SKF 538-A was negative.

Seventy-seven patients had SKF 538-A anesthesia on from 2 to 7 occasions at intervals varying from 1 to several weeks. In no instance was there any evidence of sensitivity to the drug having been produced. Some individuals claimed that postinstrumental burning and discomfort were less after the use of SKF 538-A than with nupercaine. Others could detect no difference, and still others claimed that there was less postinstrumental discomfort when no local anesthetic was used.

CONCLUSIONS

SKF 538-A is a safe, quite effective, topical anesthetic for routine use in the urethra.

In concentrations of 0.15 per cent to 0.3 per cent, SKF 538-A is a more active topical anesthetic for use in the urethra than 0.17 per cent nupercaine.

PROGRAM, ANNUAL MEETING, SOUTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION MEMPHIS, TENN., MARCH 7, 8, 9, 10, 1951

THURSDAY, MARCH 8

THE ROLE OF PROTECTIVE COLLOIDS IN THE PREVENTION OF URINARY CALCULI. Dr. Arthur J. Butt, Jr., Pensacola, Fla.
Discussed by Dr. G. Aubrey Hawes, Charlotte, N. C.

THE MANAGEMENT OF CALCULUS IN THE LOWER URETER. Drs. Champion, Fowler, Coleman and Florence (by invitation), Atlanta, Ga.
Discussed by Dr. Howell D. Woodson, Memphis, Tenn.

HYPERTENSION IN THE SURGICAL KIDNEY. Dr. Edwin P. Alyea, Durham, N. C.
Discussed by Dr. Bruno Barelare, Birmingham, Ala.

THE IMPORTANCE OF RENAL ARTERIOGRAPHY IN UPPER URINARY TRACT DIAGNOSIS. Dr. Parke Smith, Cincinnati, Ohio, Guest Speaker

POSTOPERATIVE TREATMENT FOLLOWING PROSTATIC SURGERY. Drs. James B. Glanton (by invitation), Louis M. Orr and Joseph C. Hayward, Orlando, Fla.
Discussed by Dr. Robert F. Sharp, New Orleans, La.

TRANSURETHRAL RESECTION OF THE PROSTATE. Dr. Edward H. Ray, Lexington, Ky.
Discussed by Dr. Robert Lich, Jr., Louisville, Ky.

FRIDAY, MARCH 9

A NEW FEMALE AIR CYSTO-URETHROSCOPE. Dr. David W. Goddard, Daytona Beach, Fla.
Discussed by Dr. James H. Semans, Atlanta, Ga.

SOME INTERESTING BONE CHANGES IN THE KUB. Drs. W. L. Fitzgerald and M. D. Thomas (by invitation), Miami, Fla.
Discussed by Dr. Fred K. Garvey, Winston-Salem, N. C.

RECENT TRENDS IN NEPHRECTOMY. Dr. Hugh Beacham, New Orleans, La.
Discussed by Dr. Gilbert M. Roberts, Jr., Chattanooga, Tenn.

COAGULUM PELVIOLITHOTOMY—AN IMPROVED TECHNIC. Dr. Thomas D. Moore, Memphis, Tenn. President, American Urological Association

CARCINOMA OF THE PENIS. Dr. Julio E. Colon, San Juan, Puerto Rico.
Discussed by Dr. Harold P. McDonald, Atlanta, Ga.

Past President's Address, Dr. James J. Ravenel, Charleston, S. C. THE CRISIS.

The Ballenger Memorial Lecture, Dr. John S. Lundy, Rochester, Minn. Selected Subject

NON-SPECIFIC INFECTIONS OF THE URINARY TRACT. Dr. Rudolph Bell, Thomasville, Ga.
Discussed by Dr. Eugene Park Niceley, Knoxville, Tenn.

PRIMARY SARCOMA OF THE BLADDER IN CHILDREN: A REPORT OF TWO CASES. Dr. Roger A. Way, Spartanburg, S. C.
Discussed by Dr. Frank Woods, Miami, Fla.

THORACO-ABDOMINAL NEPHRECTOMY. Drs. Jarratt P. Robertson and Sam Jameson (by invitation), Birmingham, Ala.
Discussed by Dr. W. J. McMartin, Omaha, Neb.

SATURDAY, MARCH 10

A STATISTICAL EVALUATION OF PUNCH BIOPSY OF THE PROSTATE. Drs. J. Robert Rinker and G. Warren Shuman (by invitation), Augusta, Ga.
Discussed by Dr. Paul L. Getzoff, New Orleans, La.

TORSION OF THE SPERMATIC CORD. Drs. Linus W. Hewit and E. S. Gilmer, Tampa, Fla.
Discussed by Dr. Edwin W. Brown, West Palm Beach, Fla.

SURGICAL CORRECTION OF FEMALE STRESS INCONTINENCE. Drs. Joseph E. Maurer and Robert Lich, Jr., Louisville, Ky.
Discussed by Dr. R. K. Womack, Shreveport, La.

PYELOPLASTY: AVERAGE EXPERIENCES. Drs. Charles Rieser and Charles Eberhart, Atlanta, Ga.
Discussed by Dr. William D. Watkins, Memphis, Tenn.

CALCIFIED INTRACAPSULAR RENAL HEMATOMA WITH CYSTIC DEGENERATION. Dr. T. M. Yates, Columbia, S. C.
Discussed by Dr. John R. Browning, Jacksonville, Fla.

The Journal of Urology
Vol. 65, No. 3, March 1951
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MULTILOCULAR CYSTS OF THE KIDNEY

TRUETT H. FRAZIER

From the Urological Service, Yale University School of Medicine and the New Haven Hospital, New Haven, Conn.

The subject of multilocular cyst of the kidney has been discussed relatively infrequently in the literature during the past half century. It has been recognized by many as a clinical entity; however others have regarded it as an unusual variation of the more common solitary serous cysts or of congenital polycystic renal disease. Braasch and Meland suggest that the term multilocular cyst, nevertheless, is not synonymous with polycystic disease of the kidney but refers rather to a collection of cysts within cysts, having distinct differentiating characteristics. They further believe that multilocular cysts are in no way related to polycystic renal disease or to solitary cysts but are a separate entity entirely. In setting aside multilocular renal cysts as an entity, not to be confused with polycystic kidney, Lieberthal pointed out that in polycystic disease the cysts are scattered throughout the parenchyma of both kidneys and are separated by islands of functioning renal tissue; whereas the multilocular renal cyst is unilateral and confined to some particular region of the kidney such as the hilus or one of the poles with no identifiable functioning renal tissue between the cysts. However, Lynch and Thompson as well as Dakin reported cases in which the kidney was completely replaced by a multilocular cystic mass with no identifiable renal tissue, and Schwartz reported a similar case with only a small mass of kidney tissue remaining. In the French and Italian literature, multilocular cysts of the kidney are referred to as "partially polycystic kidney"; nevertheless the disease entity is the same.

In reviewing the literature one is led to believe that multilocular renal cysts are extremely rare; although it would appear from accounts of both urologists and pathologists that the disease has been encountered either at operation or autopsy more frequently than has been previously supposed. In 1933, Braasch and Meland brought the subject up to date by reporting 6 cases from the Mayo Clinic and mentioning 4 cases previously reported in the literature (Edmonds, Haslinger, Fullerton, and Ravich), the earliest one dating back to 1892. Since 1933 there have been 7 additional cases reported in the American and Canadian literature: Schwartz, 1936; Lynch and Thompson, 1937; Lieberthal, 1939; Burrell, 1940; Dakin, 1940; Toulson and Wagner, 1942; Randolph and Murphy, 1947. In 1946 E. Chauvin referred to 9 cases of "partially polycystic kidney" in the French literature and added one case of his own. Two cases of the same disease entity have been reported in the Italian literature since 1942; so these cases along with two additional cases which will be presented in this paper bring the total number of reported cases up to 31.

The following 2 case reports are examples typical of multilocular renal cysts as encountered clinically.

PROGRAM, ANNUAL MEETING, SOUTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION
MEMPHIS, TENN., MARCH 7, 8, 9, 10, 1951

THURSDAY, MARCH 8

The Role of Protective Colloids in the Prevention of Urinary Calculi. Dr. Arthur J. Butt, Jr., Pensacola, Fla.
Discussed by Dr. G. Aubrey Hawes, Charlotte, N. C.

The Management of Calculus in the Lower Ureter. Drs. Champion, Fowler, Coleman and Florence (by invitation), Atlanta, Ga.
Discussed by Dr. Howell D. Woodson, Memphis, Tenn.

Hypertension in the Surgical Kidney. Dr. Edwin P. Alyea, Durham, N. C.
Discussed by Dr. Bruno Barelare, Birmingham, Ala.

The Importance of Renal Arteriography in Upper Urinary Tract Diagnosis. Dr. Parke Smith, Cincinnati, Ohio, Guest Speaker

Postoperative Treatment Following Prostatic Surgery. Drs. James B. Glanton (by invitation), Louis M. Orr and Joseph C. Hayward, Orlando, Fla.
Discussed by Dr. Robert F. Sharp, New Orleans, La.

Transurethral Resection of the Prostate. Dr. Edward H. Ray, Lexington, Ky.
Discussed by Dr. Robert Lich, Jr., Louisville, Ky.

FRIDAY, MARCH 9

A New Female Air Cysto-Urethroscope. Dr. David W. Goddard, Daytona Beach, Fla.
Discussed by Dr. James H. Semans, Atlanta, Ga.

Some Interesting Bone Changes in the Kub. Drs. W. L. Fitzgerald and M. D. Thomas (by invitation), Miami, Fla.
Discussed by Dr. Fred K. Garvey, Winston-Salem, N. C.

Recent Trends in Nephrectomy. Dr. Hugh Beacham, New Orleans, La.
Discussed by Dr. Gilbert M. Roberts, Jr., Chattanooga, Tenn.

Coagulum Pelviolithotomy—An Improved Technic. Dr. Thomas D. Moore, Memphis, Tenn. President, American Urological Association

Carcinoma of the Penis. Dr. Julio E. Colon, San Juan, Puerto Rico.
Discussed by Dr. Harold P. McDonald, Atlanta, Ga.

Past President's Address, Dr. James J. Ravenel, Charleston, S. C. The Crisis.

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Discussed by Dr. Edwin W. Brown, West Palm Beach, Fla.

Surgical Correction of Female Stress Incontinence. Drs. Joseph E. Maurer and Robert Lich, Jr., Louisville, Ky.
Discussed by Dr. R. K. Womack, Shreveport, La.

Pyeloplasty: Average Experiences. Drs. Charles Rieser and Charles Eberhart, Atlanta, Ga.
Discussed by Dr. William D. Watkins, Memphis, Tenn.

Calcified Intracapsular Renal Hematoma with Cystic Degeneration. Dr. T. M. Yates, Columbia, S. C.
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In reviewing the literature one is led to believe that multilocular renal cysts are extremely rare; although it would appear from accounts of both urologists and pathologists that the disease has been encountered either at operation or autopsy more frequently than has been previously supposed. In 1933, Braasch and Meland brought the subject up to date by reporting 6 cases from the Mayo Clinic and mentioning 4 cases previously reported in the literature (Edmonds, Haslinger, Fullerton, and Ravich), the earliest one dating back to 1892. Since 1933 there have been 7 additional cases reported in the American and Canadian literature: Schwartz, 1936; Lynch and Thompson, 1937; Lieberthal, 1939; Burrell, 1940; Dakin, 1940; Toulson and Wagner, 1942; Randolph and Murphy, 1947. In 1946 E. Chauvin referred to 9 cases of "partially polycystic kidney" in the French literature and added one case of his own. Two cases of the same disease entity have been reported in the Italian literature since 1942; so these cases along with two additional cases which will be presented in this paper bring the total number of reported cases up to 31.

The following 2 case reports are examples typical of multilocular renal cysts as encountered clinically.

CASE REPORTS

*Case 1.** K. B., a male child 3½ years of age, was admitted to the pediatrics service of the New Haven Hospital on November 29, 1933 because of a mass in the left upper quadrant of the abdomen discovered by his family physician on routine physical examination. It was revealed by the patient's mother that there had been no previous signs or symptoms of urinary tract disease other than enuresis since birth. There was no history of pain or hematuria.

The patient did not appear ill. Temperature 100 F, pulse 100, respirations 24, B. P. 100/60. On examining the abdomen a tumor mass measuring 8 by 10 cm. was found to fill the left upper abdomen and flank. The mass was smooth, nontender, elastic in consistency, and somewhat movable. The left kidney could not be distinguished from the mass. The urine showed 1 plus albumin and fatty casts. Red blood cells 5.2 million, white blood cells 11,000 with a normal differential. Phenolsulfonphthalein excretion 55 per cent in 1 hour. Nonprotein nitrogen 33 mg. per cent. The lower urinary tract was normal on cystoscopy. Retrograde pyelo-ureterograms revealed a normal kidney and ureter on the right: however there was a marked pressure deformity of the renal pelvis and the middle and lower calyces on the left. A large soft tissue mass involved the lower pole of the left kidney (fig. 1). The phenolsulfonphthalein excretion was normal from

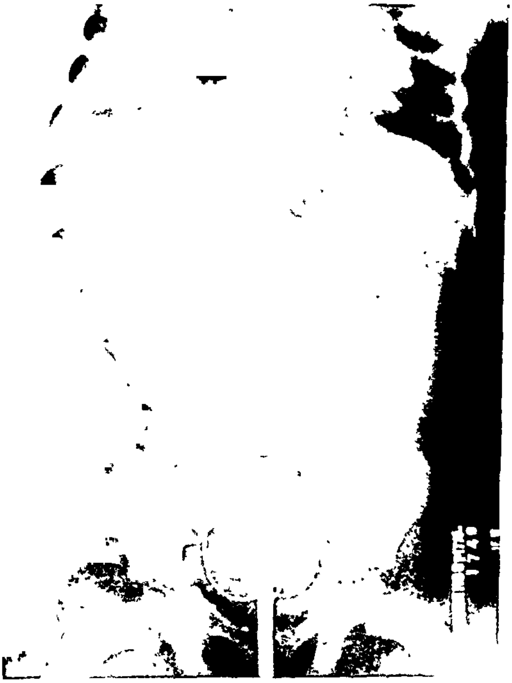

FIG. 1. Case 1. Retrograde pyelograms showing large left flank mass with deformity of left renal pelvis and calyces.

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* The report of case 1 is incorporated with the permission of Dr. Clyde L. Deming, clinical professor of urology, Yale University School of Medicine.

the right kidney and absent from the left kidney in 15 minutes. Metastatic x-ray series was negative.

A tentative diagnosis of Wilms tumor was made, and the patient was given a course of deep x-ray therapy. After 5 weeks it was found that the size of the tumor had decreased only slightly and still presented the previously described characteristics.

On February 6, 1934 the left kidney was explored by Dr. Deming through a flank incision, and a rounded tumor mass with a smooth, glistening, white capsule was found to involve the entire lower half of the kidney (fig. 2). The tumor measured 12 cm. in diameter and along with the kidney was easily dissected free from surrounding structures and removed. The patient made an uneventful recovery.

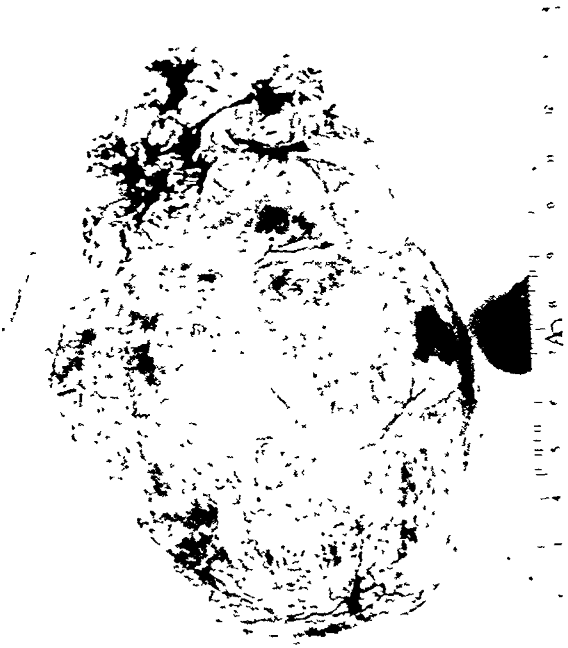

FIG. 2. Case 1. Gross specimen. Notice marked similarity to solid tumor

Upon sectioning the specimen, the greater part of the mass was seen to be composed of a well circumscribed, encapsulated, multilocular tumor measuring 8 by 10 cm. The capsule measured 2–4 mm. in thickness, and from this arose numerous thin-walled septa which subdivided the mass into numerous irregular cystic cavities containing a clear almost jelly-like material and having the appearance of a pseudomucinous cyst. Most of the kidney tissue had been obliterated by the encroachment of the cystic tumor, there remaining only the superior pole of the kidney which measured 2 by 5 cm. and appeared normal grossly (fig. 3).

Microscopic study of sections of tissue taken from the superior pole of the specimen revealed normal renal tissue except near the border between the renal tissue and the cystic structure, where a number of hyalinized glomeruli and compressed renal tubules with slight round cell infiltration in an increased connective tissue stroma were seen. The cyst wall which appeared to have been formed by compression of surrounding renal tissue was made up for the most part by a dense hyalinizing fibrous connective tissue (fig. 4). The lumina of the cysts or locules were filled with a light pink staining material, and the cysts were lined by a cuboidal and in some cases flattened epithelium (fig. 5). The walls of some locules showed papillary in-foldings; however these were coarse and were covered by a single layer of flattened epithelial cells. No evidence of malignancy was noted. Final diagnosis: Multilocular cyst of left kidney.

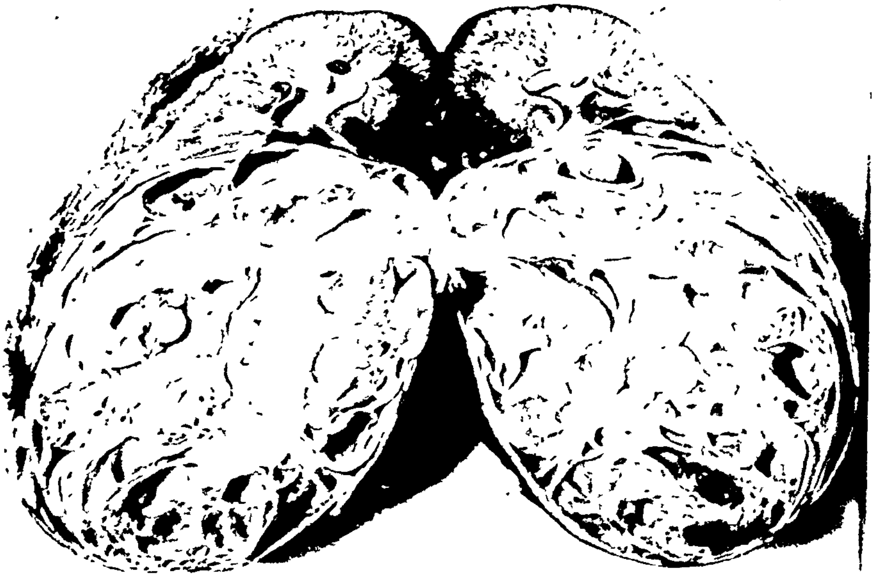

FIG 3 Case 1. Gross specimen sectioned. Notice gross resemblance to cystadenoma. Thick capsule separates cystic mass from normal upper pole of kidney.

During the past 16 years this patient has been followed closely as an out-patient. In the spring of 1949, the patient, then 19 years of age, was found to have an average blood pressure of 150/106. More recent examination has confirmed the persistence of hypertension which responds only moderately to cold pressor and sedation tests. The urine was normal as were the phenolsulfonphthalein excretion and the nonprotein nitrogen. Urine concentration tests showed a maximum specific gravity of 1.017. Pyelographic studies of the remaining right kidney revealed no abnormalities. No definite evidence is present at this time that the patient's hypertension is in any way related to disease in his remaining right kidney.

Case 2. On April 19, 1949, S. A. M., a 6 months old male child was admitted to the pediatrics service of the New Haven Hospital, his mother revealing that she had noticed "rusty urine" stains on his diapers and a "lump" in the left upper abdomen while bathing him 4 days prior to admission. There had been no previous evidence of urinary tract disease.

On examination the patient appeared to be in excellent health. Temperature 100 F, pulse 140, respirations 22, B. P. 106/60. Inspection of the abdomen revealed a large, bulging mass occupying the left upper abdomen and flank and moving on respiration. The mass was nontender, presented a smooth surface except for a shallow cleft on its anterior surface, and was rubbery in consistency. The liver, spleen, and right kidney were not palpable.

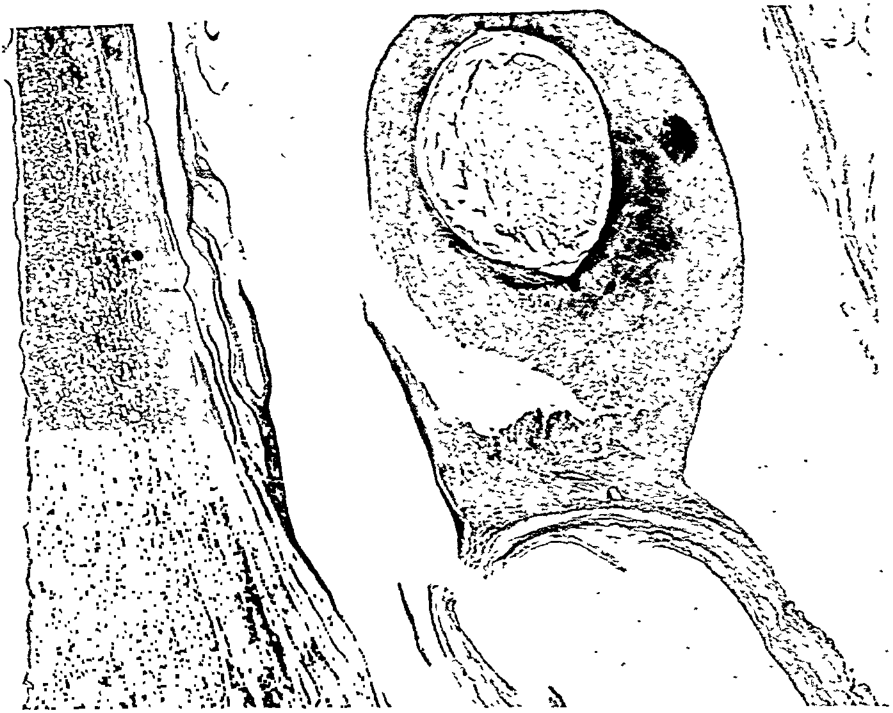

FIG. 4. Showing compression of adjacent renal tissue by thickened fibrous capsule of cyst. H. & E. stain, × 5.

The urine showed 2 plus albumin with 0–8 red blood cells. Red blood cells 5.07 million; white blood cells 17,800 with 34 segmented forms, 60 lymphocytes, and 6 monocytes; nonprotein nitrogen 21 mg. per cent. CO_2-22 meq./liter; CL-99.6 meq./liter. A metastatic x-ray series was negative. Excretory urography revealed a large, spherical, soft tissue mass roughly 10 cm. in diameter in the left upper abdomen which appeared to arise from the lower pole of the left kidney. The mass was homogeneous in appearance and without calcification. The adjacent intestinal loops were displaced medially, anteriorly, and inferiorly. The right kidney appeared normal. In the left kidney the inferior and middle calyces appeared dilated, flattened, and displaced upward (fig. 6). On the lateral projection the mass could be seen encroaching on the anterior wall of the renal pelvis producing flattening. A diagnosis was made of tumor of the left kidney, probably of the variety described by Wilms.

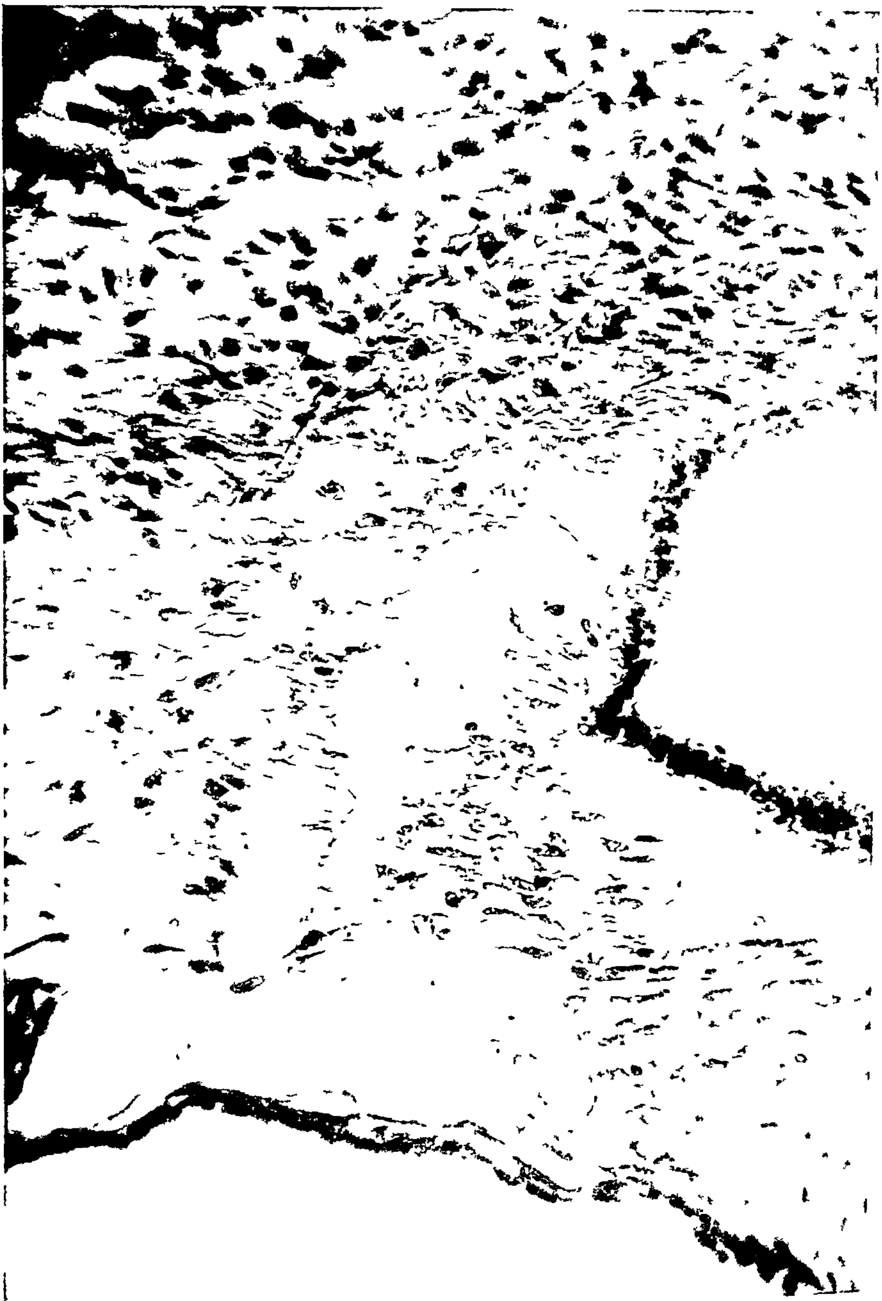

FIG 5 Case 1 Individual cysts are lined with both cuboidal and flattened epithelium Septa are of dense connective tissue H & E stain, × 13

Consequently on April 22, 1949, the third day of hospitalization, the left renal region was explored through an incision extending in the midline from the xiphoid process to a point 2 cm. above the umbilicus, thence laterally and posteriorly to the left costovertebral angle. Through a transperitoneal approach a well encapsulated tumor mass, approximately 12 cm. in diameter, involving the lower pole of the left kidney, was encountered. The process had all the appearances of a neoplasm; therefore, after finding the right kidney palpably normal, a left nephrectomy was carried out. There was no evidence of lymph node involvement in the region of the pedicle. Postoperative recovery was rapid and uncomplicated.

The specimen consisted of a kidney measuring 13 by 9 cm., the lower pole of which was replaced by a large tense mass which beneath the thickened capsule appeared lobulated. The superior pole appeared to be grossly normal kidney. On opening the mass one noticed 50–60 closely packed, thin walled, translucent cysts containing clear fluid. This group of cysts was in turn surrounded by a somewhat thicker wall or capsule, which varied in thickness from 2–4 mm., and which separated the mass of cysts from the upper pole of grossly normal kidney. The diameter of the individual cysts or locules varied from 0.5–4 cm. The gross picture of this specimen was remarkably similar to that in the previous case report (figs. 2 and 3).

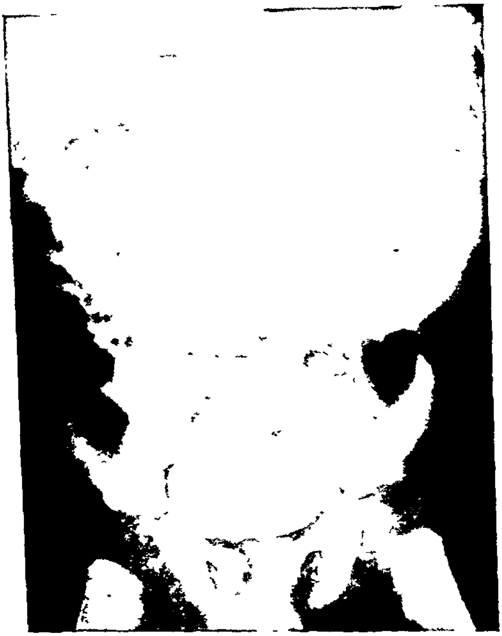

FIG. 6. Case 2. Excretory urogram showing large mass in left flank displacing left ureter to right side of abdomen with marked deformity and upward displacement of left renal pelvis and calyces.

Microscopic sections through the capsule of the mass showed rather primitive looking connective tissue consisting of fibroblasts with large oval nuclei and large amounts of fibrillar cytoplasm and being infiltrated with numerous lymphocytes (fig. 7, A). The multiple cysts contained within were supported by a similar primitive-looking, very loose stroma perforated by many capillaries. These septa

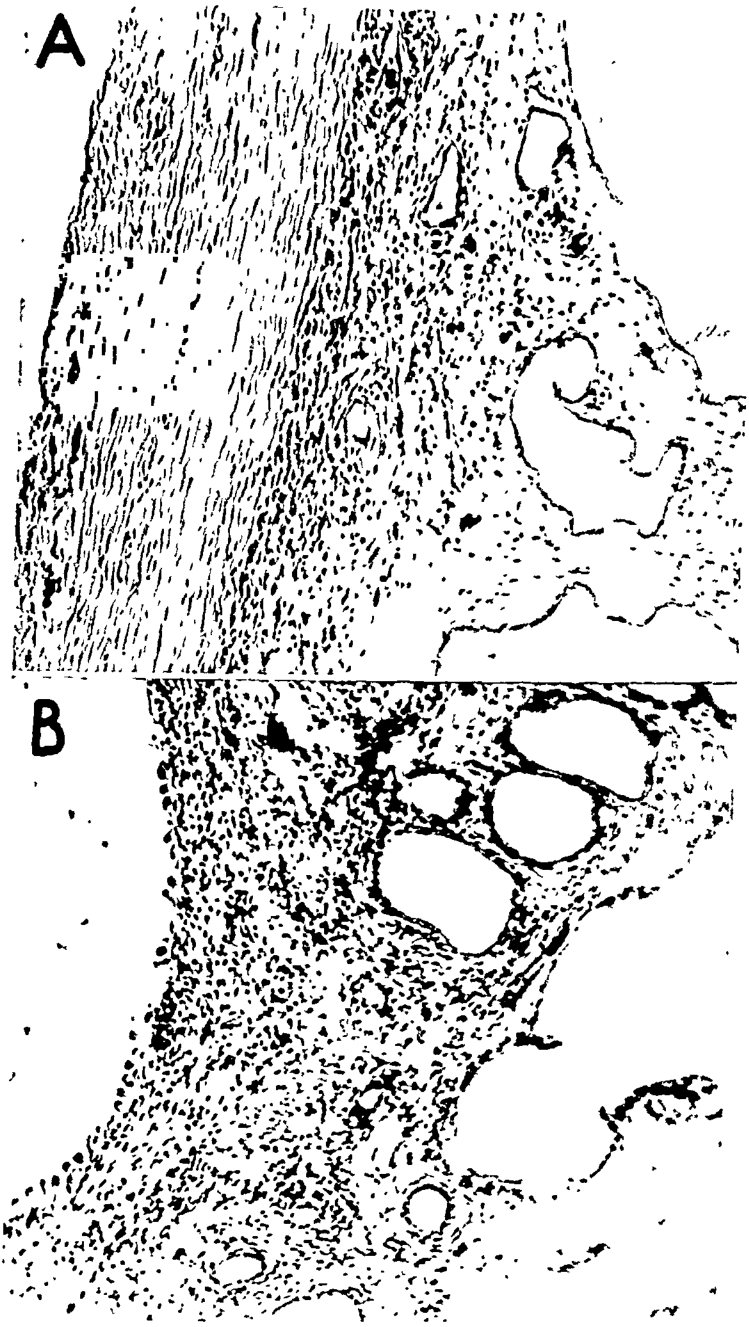

FIG. 7. Case 2. *A*, showing thick fibrous tissue capsule of cyst and primitive looking loose fibrous stroma of septa H & E stain, × 10. *B*, cysts are lined with both flat and cuboidal epithelium. Notice dilated tubules (? small beginning cysts) in septa.

were quite thin and not perforated. They contained scattered epithelial elements which had the appearance of tubules, somewhat dilated, in some sections (fig. 7, *B*). Some of the cysts were lined by a very low cuboidal epithelium, others being lined by irregular epithelium having large cells with irregular outlines and large oval nuclei, appearing to be some phase of a transitional epithelium (fig. 7, *A* and *B*). A few cysts contained both types of epithelium. Sections through the renal tissue of the upper pole revealed normal kidney except in the areas adjacent to the capsule of the multilocular cyst which showed compression of the tissue and increased fibrous stroma with numerous infiltrating lymphocytes. No evidence of malignancy was noted. Diagnosis: Multilocular cyst of the kidney.

The patient has been followed in the out-patient department during the past 6 months. Recent excretory urograms reveal a normal right kidney.

DISCUSSION

It is obvious to the reader of these 31 various case reports that each case presents certain features which differ from the others; however, they are for the most part similar and meet the basic criteria for classifying them as multilocular cysts, i.e., two or more chambers to the cyst, the separating walls of which are complete and the over all arrangement of which is dissimilar grossly at least to congenital polycystic disease of the kidney, solitary renal cysts, and multiple cystic disease of the kidney. In most of the cases reported, the mass was confined to one particular area of the kidney such as the hilus or one of the poles. In 4 cases the cystic masses contained dozens of small cysts, the entire group of which was incorporated within a relatively thickened capsule, presenting a picture suggesstive of cystadenoma of the kidney. As yet the disease has not been found to occur bilaterally, but in some of the cases associated changes such as solitary serous cyst, simple retention cysts, nephritis, infarction, or tuberculous nephritis was found in the same kidney. Hepler, in reviewing the literature, found that the average age incidence of simple serous cysts is 45 years with an occurrence two times as frequent in the female as in the male. In the reported cases of multilocular renal cysts all age groups are represented, but half the cases occurred in children under the age of five years, the youngest case reported being discovered clinically at the age of 4 days. The remaining cases occurred in individuals between the ages of 22 and 71 years. The incidence is equal in males and females.

Both solitary cysts of the kidney and polycystic renal disease are encountered clinically with relative infrequence, the former being very rare in children and infants. It is estimated by Branch that solitary cysts of the kidney occur in 3–5 per cent of all autopsies. The markedly low incidence of multilocular renal cysts is demonstrated by the fact that during the past 15 years only 2 cases of the entity have been encountered clinically at the New Haven Hospital in a total of 8,060 urological admissions. During the same time interval 8 cases of polycystic renal disease and 52 cases of solitary serous cyst were diagnosed clinically in hospitalized patients.

The relation of multilocular cysts to solitary serous cysts and polycystic rena disease is as yet not known. It seems logical, nevertheless, to suppose that thl origin of all three is similar. The demonstration of tubular epithelial elements ie the septa separating the multiple locules in case report number 2 above suggests that multilocular cysts may indeed be an unusual variation of the more common polycystic renal disease.

The etiology of renal cysts is still an unsettled point. In general it is thought that renal cysts are either congenital, acquired, or neoplastic in origin. The theories concerning congenital origin are centered chiefly around: 1) embryonal rests from the renal blastema which belatedly form disconnected cavities; 2) retention cysts secondary to constriction of tubules by fibrous tissue; 3) the failure of union between the filtration-secretory portion of the kidney, derived from the renal blastema, and the collecting ducts, derived from the wolffian duct (Hildebrandt); 4) the persistence of the cystic or vesicular stage in the development of renal tubules in the foetus and their later expansion (Kampmeier).

Kampmeier, in support of his theory states, "... every human individual during his foetal life normally passes through a period characterized by the presence of numerous cystic renal tubules. Such a normal physiological event, however, may be converted into an abnormal or pathological condition if such tubules do not give way at the end of their allotted time but continue to grow and expand to the detriment of adjacent normal structures." Today, the "failure of union" theory of Hildebrandt is probably the most commonly accepted theory regarding the origin of congenital renal cysts. Frazer supports this theory by postulating that it is the failure of junction between the pelvic portion of the growing kidney and the metanephric blastema which may lead to the many varieties of congenital cystic kidney. As pointed out by Davis, such a process limited to a small nest of renal tissue could reasonably give rise to the uncommonly seen multilocular cysts of the kidney.

Hepler, one of the chief proponents of the "acquired" theory, states, "These large usually solitary cysts of the kidney are acquired. They are not a distinct entity with a common etiology, but the mechanism of their production is essentially the same. Recognized pathological conditions of the kidney cause them, but only when so situated as to produce a combination of group tubular obstruction and anaemic degeneration of the parenchyma from circulatory disturbances, in the same segment of the kidney." In support of this theory he was able, by blocking the tubules of the rabbit's kidney through fulguration of the papilla, in combination with the ligating of the posterior branch of the renal artery, to produce a cyst in the infarcted area similar in every way to the commonly encountered solitary cyst of the kidney.

Other observers contend that solitary cysts, particularly hemorrhagic cysts, result from the cystic degeneration of neoplasms. The acquired origin of the simple retention cysts seen in chronic nephritis and associated with cicatricial changes in the tubules is well recognized and is of no great clinical importance.

Campbell points out that multilocular cysts may be considered as an aggregation of solitary cysts and is probably of the same etiology. Along the same line it is set forth by McCrea that: "Multilocular cysts are identical with solitary serous cysts except that the cysts are multiple." Lynch and Thompson state that: "Large solitary cysts are possibly the later stages of multilocular cysts whose walls and septa become obliterated as the sole great cavity was formed." A multilocular cyst might be considered then as a form in which fusion and obliteration of the septa or walls of the individual cysts have not taken place. Whether the process represents an aggregation of solitary cysts or a single cyst with a multiloculated cyst wall is not clear.

The symptoms of multilocular cyst of the kidney are similar to those of solitary serous cysts and depend mainly on size and situation of the cyst. The symptoms and signs most frequently presented are mass in one of the flank regions, gross hematuria, pain, and infected urine. It is interesting to note that in infants and young children the presenting symptom is usually a palpable mass associated in some cases with gross hematuria. These findings, coupled with the x-ray picture and the fact that solitary and multilocular cysts of the kidney are very rare in this age group, makes it quite understandable that in almost every case reported a preoperative diagnosis of Wilms tumor was made. It is of further interest to note that in none of the reported cases of multilocular cyst of the kidney was the diagnosis made preoperatively in any age group.

The treatment of choice is surgery. In most of the reported cases a nephrectomy was done. Fey and Ferrier reported the successful extirpation of a multilocular cyst from a sole remaining kidney in a 50 year old woman, the other kidney having been removed several years previously because of infection. Since there is no evidence that the process is associated with malignant tumor, conservative therapy by simple extirpation of the cyst wherever practical and possible seems advisable.

In the first case reported in this article, the patient, who 16 years ago underwent nephrectomy for multilocular cyst of the left kidney, now at the age of 19 years is found to have hypertension with an average blood pressure of 150/106, but no pyelographic or physiological evidence of cystic disease of the remaining kidney. The bilateral nature of polycystic renal disease and its association with hypertension and altered renal physiology is well recognized. As yet no cases of either bilateral multilocular renal cysts or of hypertension definitely associated with multilocular cysts of the kidney have been reported. The absence of such reports does not preclude the possibility of their occurrence, however. It is felt by the author that all cases of multilocular cystic disease of the kidney should be carefully followed for subsequent development of the same or a related cystic process in the opposite kidney. The relationship of the disease to hypertension is not known, but, follow up reports on all cases encountered should in time settle the question.

If, within a reasonable time (15 to 30 years) following surgical treatment for unilateral multilocular cysts of the kidney, it is found that as a rule these cases do develop arterial hypertension and altered renal physilogy without other explanation, one would be forced to rule out the same or a similar cystic disease in the remaining kidney substance. If such cystic changes should be demonstrated by radiological examination, at operation, or at autopsy, one might be justified in concluding that multilocular cystic disease of the kidney is very closely allied to congenital polycystic renal disease.

SUMMARY

Multilocular cyst of the kidney is a clinical and pathological entity not to be confused with the more common polycystic renal disease and large solitary serous cysts.

Two case reports of multilocular cyst of the kidney have been presented.

The etiology of renal cysts in general is an unsettled point; various theories regarding renal cyst formation have been presented.

The relationship between multilocular renal cyst, polycystic renal disease, and large solitary serous cysts of the kidney is not clear. However it seems logical to assume that they represent different manifestations of a common etiological factor, probably congenital in nature.

Multilocular cyst of the kidney is rare, only 31 cases having been reported in the literature, and all of these occurring unilaterally. All age groups were represented with half the cases occurring in children under the age of 5 years, the youngest being 4 days of age. Only 2 cases of the disease were encountered at the New Haven Hospital over a 16 year period from a total of 8,060 urological admissions.

It is difficult to correctly diagnose the disease preoperatively as evidenced by the fact that in none of the 31 reported cases was the correct diagnosis made preoperatively.

In children and infants the disease closely simulates Wilms tumor clinically, and this has been the usual preoperative diagnosis in this age group.

Multilocular cyst should be considered as a differential diagnosis in children under the age of 5 years when a unilateral mass involving the kidney with or without gross hematuria is found clinically.

The symptoms of this disease are in general similar to those of solitary serous cyst, namely: mass in flank, pain, hematuria, and infection, depending mainly on the size and situation of the cyst.

The treatment of choice is surgical extirpation of the cyst if possible and practical; if not, nephrectomy should be done.

The author suggests a long-term follow-up of each diagnosed case of multilocular cysts of the kidney in order to determine the possible but heretofore unreported occurrence of the same or a related cystic process in the opposite kidney, and the possible relationship of this disease to the subsequent development of arterial hypertension in some of these cases.

If the occurrence of arterial hypertension and altered renal physiology coupled with the proof of existing cystic disease in the remaining kidney should prove to be the rule in these cases, it would strongly suggest that multilocular cystic disease is closely allied to congenital polycystic disease.

U. S. Veterans Administration Hospital, Newington 11, Conn.

REFERENCES

Beer, E.: Ann. Surg., **76:** 656, 790, 1922.

Branch, C. F.: J. Urol., **21:** 451–453, 1929.

Burrell, N. L.: J. Urol., **43:** 656–663, 1940.

Campbell, M. F.: Pediatric Urology. New York: Macmillan Co., **1:** 201, 1937.

Carson, W. J.: Ann. Surg., **87:** 250, 1928.

Chauvin, E.: J. d'urol., **52:** 210–213, 1944–1945.

Dakin, W. A.: Canad. M.A.J., **42:** 531–533, 1940.

Edmunds, W.: Lancet (Tr. Path. Soc. London), **1:** 801, 1892.

Fey, B. and Ferrier, L.: Mem Acad. de Chir., **65:** 1294–1298, 1939.

Frazer, J. E.: A Manual of Embryology: The Development of the Human Body. New York: Wood, 1932.

Hepler, A. B.: Surg. Gynec. & Obst., **50:** 660–687, 1930.

Hepler, A. B.: J. Urol., **44:** 206, 1940.

Hildebrandt, O.: Arch. f. klin. chir., **48:** 343–371, 1894.

Kampmeier, O. F.: Surg. Gynec. & Obst., **36:** 208–216, 1923.

Lieberthal, F.: J. Urol., **42:** 321–325, 1939.

Lynch, K. D. and Thompson, R. F.: J. Urol., **38:** 58–60, 1937.

McCrea, L. E.: Clinical Urology, Essentials of Diagnosis and Treatment. Philadelphia: F. A. Davis Co., 1946, p. 289.

Mutoni, E.: Arch. ital. urol., **19:** 307–319, 1942.

Randolph, M. and Murphy, F. J.: Clin. Proc. Child. Hosp., **3:** 248–251, 1947.

Ravich, A.: J. Urol., **25:** 223–234, 1931.

Schwartz, J.: J. Urol., **35:** 259–263, 1936.

Toulson, W. H. and Wagner, J. A.: Bull. School Med. Univ. Maryland, **26:** 177–184, 1942.

Zagmoni, C.: Friuli med., **1:** 51–52, 1946.

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DISSECTING ANEURYSM OF THE ABDOMINAL AORTA SIMULATING RENAL DISEASE: A CASE DIAGNOSED ANTE-MORTEM

HENRY A. KONTOFF AND BERNARD R. SEARS

Rupture of a dissecting aneurysm of the aorta may give rise to symptoms and signs simulating urinary lithiasis and other urological lesions, such as perinephric abscess, infarct of the kidney and renal tumor. In cases where there is slow leakage of blood from the ruptured aneurysm, life may go on for weeks and months before the fatal rupture occurs, but if the rent in the aneurysm is a large one, death occurs in 2 to 6 days.

The most common causes of aneurysm are syphilis and arteriosclerosis. It is generally agreed that those of syphilitic origin usually occur in the arch and thoracic portion of the aorta and occur in the younger age groups, while the aneurysms due to arteriosclerosis occur in the abdominal aorta and are usually of the dissecting type and present themselves in an older age group. The lesion is predominant in the male.

The signs and symptoms directing attention to the urinary tract arise from rupture into the retroperitoneal space or from occlusion or dissection of the walls of the renal artery; at times, secondary complete or partial thrombosis of the artery may also be present. The entire retroperitoneal space from the diaphragm to the pelvis may be distended with blood clot, causing displacement of important abdominal structures. When the hemorrhage into the perirenal area is sudden and massive, a flank mass may be found, together with tenderness, spasm, and a pulsation and bruit. Pressure on the nerve roots by the aneurysmal sac may also produce pain in the renal area.

Classically, dissecting aneurysm of the aorta presents a striking clinical picture with pain, collapse, and manifestations of vascular compression as the dominant features. The onset is characterized by sudden abdominal pain, transient syncope, dyspnea, circulatory collapse and prostration. The pain, starting in the upper abdomen, flank, or midback, often radiates downward. Arterial compression may produce paraplegia, monoplegia, intestinal paresis, hematuria, and, at times, anuria. One or both femoral pulsations may be absent, sometimes returning after re-perforation into the arterial channel. Blood pressure may be elevated, low or at normal levels. Pallor and increasing anemia are present. There may be nausea and vomiting, fever, leukocytosis, and albuminuria. The blood picture is that of typical secondary anemia.

The urological findings are varied. There may be impaired excretion of diodrast due to renal ischemic anoxia or due to interference with urinary drainage by direct pressure of the hematoma on the pelvis or ureter. Often there is obliteration of the psoas shadow. Depending on the quantity and distribution of the blood clot, the kidney may be rotated on its vertical or transverse axis and displaced laterally, upward or downward. There may be haziness or irregularity of the

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Read at the meeting, New England Section, American Urological Association, Boston, Mass., March 23, 1950.

calyceal, pelvic or ureteral outline because of blood clot; a subsequent x-ray may show the disappearance of this abnormality if the clot has passed. Approximately 33 per cent of cases reported in the literature had hematuria. Hematuria usually signifies involvement of the renal artery.

To recapitulate, the important signs and symptoms for consideration that are significant to the urologist in making a diagnosis of dissecting aneurysm of the abdominal aorta are:

1) Sudden pain in the upper abdomen, flank, or midback. This pain is constant and does not appreciably yield to the ordinary opiates.

2) Faintness, pallor and increasing anemia which are not improved with repeated blood transfusions.

3) Urographic changes that are usually seen in the malposition of the kidney and ureter, impaired function of the kidney, and obliteration of the psoas margin.

4) Loin mass that has a pulsation and bruit.

CASE REPORT

No. 23584, Orin K., a 70 year old retired rivet maker, entered the hospital with the chief complaint of severe left back and flank pain. Two days before admission, while seated in his bath tub and bending forward to wash his feet, the patient felt "something snap" with a sudden sharp pain in his left back. The pain was so severe that he could not leave the tub without assistance. His family physician strapped his back with adhesive tape, believing the patient had strained his back muscles. Four hours later the pain radiated to the left flank and abdomen. Seven hours after the initial attack of pain his abdomen became distended. He had no nausea but vomited once. The patient had episodes of extreme weakness. Because of the abdominal distention, extreme weakness and increase in back and flank pain, the patient was hospitalized.

The past history was essentially negative except for infectious diseases of childhood. He had had no operations or accidents. System review revealed that his blood pressure was 160/80 for the past few years. There were no urinary symptoms.

Physical examination revealed a well developed and well nourished white man, with pallor of his skin and in some discomfort. The temperature was 98F, pulse 98, respirations 20, blood pressure 125/70. Head, neck, heart, and lungs were not remarkable. The abdomen was distended and tympanitic throughout, no masses felt nor abnormal sounds heard by stethoscope. The patient complained of tenderness to palpation in the left upper quadrant of the abdomen, left flank, and left costovertebral angle. Neither kidney could be felt. The genitalia were normal. The rectal examination revealed the prostate to be normal in size and consistency.

The laboratory reported the urine clear; pH 5.5; albumin negative; sugar negative; acetone negative; bile negative; sediment showed a few white blood cells and occasional red blood cells per high power field and uric acid crystals. Red blood cells 2,900,000; white blood cells 20,000; hemoglobin 53 per cent (7.7 gm. per cent). Polymorphonuclears 81 per cent; lymphocytes 13 per cent;

stabs 6 per cent, achromia of red blood cells. Hinton and Kahn tests negative. The plain x-ray of the abdomen showed "the entire colon dilated with gas and with considerable amount of fecal material in the ascending colon. The kidney outlines were obscured by intestinal shadows. There was an opacity overlying the region of the left kidney that might represent a renal calculus."

For 36 hours after admission, the patient was given sedatives but they gave only temporary relief and the pain persisted in the left costovertebral angle, left flank and finally radiated to the lower left abdomen. Repeated enemas did not relieve the abdominal distention. The patient ate his meals without nausea or vomiting. The hospital staff considered the diagnosis of left renal calculus and asked for a urological consultation.

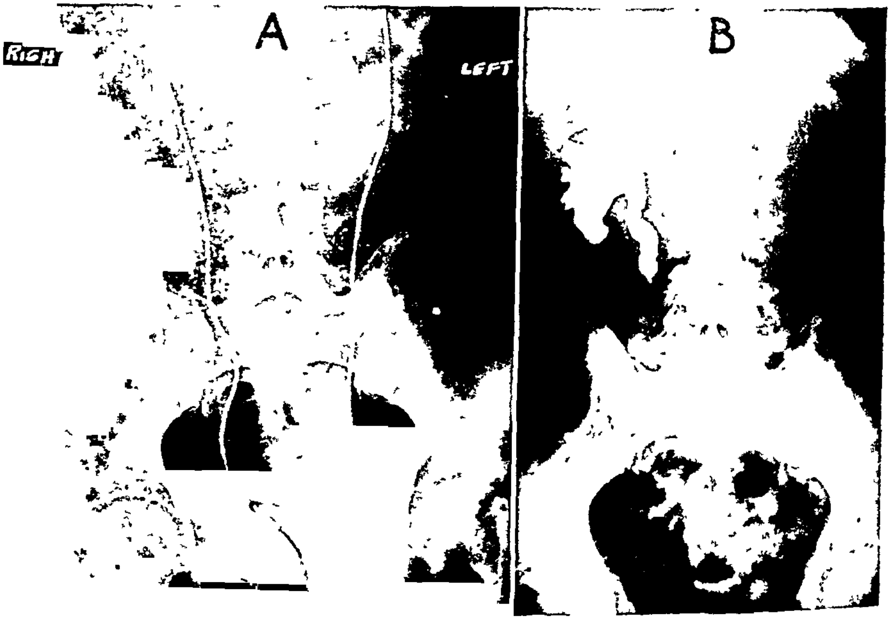

Fig. 1. *A*, plain x-ray with ureteral catheters in place revealing lateral displacement of upper two thirds of left ureter. *B*, retrograde pyelograms reveal normal architecture of both kidneys. Left kidney is displaced upward and laterally and upper left ureter is displaced laterally by a large retroperitoneal tumor.

Cystoscopic examination revealed the bladder mucosa to be normal throughout; no stones, tumor or diverticula seen. A No. 5 catheter passed up both ureters without meeting obstruction and there was clear flow of urine from each kidney. A plain x-ray (fig. 1, *A*) showed marked lateral displacement of the upper two thirds of the left ureter. No calculi were seen in the urinary tract. The retrograde pyelogram (fig. 1, *B*) showed the calyces and pelves of both kidneys to be normal in outline. The position of the right kidney and ureter was normal. The left kidney was displaced upward and to the left. The upper two thirds of the left ureter was displaced about 6 cm. laterally by a large retroperitoneal mass.

A diagnosis of rupture of a dissecting aneurysm of the abdominal aorta was made.

Whole blood and plasma were given without any appreciable gain in the blood count. No amount of sedation seemed to relieve the patient of pain which seemed to increase in severity. On the third day after admission to the hospital, the patient suddenly complained of excruciating pain in left lower quadrant of his abdomen, went into shock and died within a few minutes.

On post mortem examination "the aorta shows marked calcification. Midway between the diaphragm and the bifurcation of the iliac vessels, there is an area of rupture. The aorta adjacent to the area of rupture measures 8.5 cm. in diameter, and there is a dissecting aneurysm in this region, which condition has existed for a long period of time, evidenced by laminated clot in the aneurysmal sac. The aneurysm has ruptured on the left side and there is a massive hemorrhage into the left retroperitoneal tissues."

SUMMARY

A review is made of the clinical picture of dissecting aneurysm of the abdominal aorta, with special reference to manifestations directing attention to the urinary tract.

A case, diagnosed ante-mortem by means of urological study, is reported.

483 Beacon St., Boston, Mass.

REFERENCES

Bauersfeld, S. R.: Ann. Int. Med., **26:** 873, 1947.
Blakemore, A. H.: Ann. Surg., **126:** 195, 1947.
Blain, A. and Glynn, T. P.: J. Urol., **53:** 753, 1945.
Buckley, T. L.: J. Urol., **44:** 816, 1940.
David, P. et al.: Ann. Int. Med., **27:** 405, 1947.
Greene, L. F.: J. Urol., **59:** 174, 1948.
Lazarus, J. A. and Marks, M. S.: J. Urol., **52:** 115, 1944.
Perry, T. M.: Am. Heart J., **12:** 650, 1936.
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Uhle, C. A. W.: J. Urol., **45:** 13, 1941.

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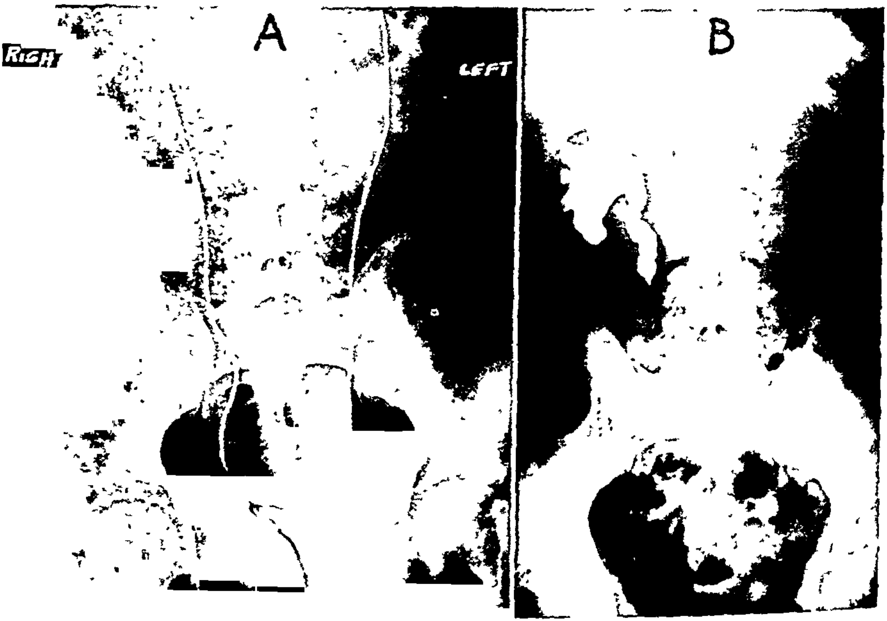

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DIAGNOSIS OF INVOLVEMENT OF INFERIOR VENA CAVA IN RENAL NEOPLASMS

P. A. DUFF AND W. H. GRANGER

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Involvement of the inferior vena cava, with partial or complete obstruction, is not uncommonly associated with renal neoplasms. The subject has been thoroughly discussed and the literature reviewed by several authors, notably Pleasants (1911), Simpson (1924), Hyman and Leiter (1938) and Ney (1946). Ney found 41 previously reported cases of tumor thrombosis of the inferior vena cava associated with renal neoplasm in the literature and added 10 more cases. He did not include the 11 cases reported by Hyman and Leiter.

The diagnosis of thrombosis of the inferior vena cava is rarely made clinically, according to Ney, because of the scarcity of signs. The condition was recognized in most of Hyman and Leiter's cases at operation. Edema of one or both legs that occurs at some time during the course of the disease is the most common sign associated with thrombosis of the inferior vena cava. Other signs such as collateral circulation are sometimes noted, but this manifestation can be completely absent superficially because the deep collaterals are the ones mainly involved. Our purpose here is to discuss a method by which the diagnosis of this condition can be made with accuracy and perhaps be of benefit to both the patient and the surgeon.

During the past year 2 cases of renal neoplasm with extensive involvement of the inferior vena cava have come to our attention. Both had typical pyelographic, physical, and laboratory findings of malignant tumor of the right kidney. Neither patient on admission showed any evidence of distant metastases, edema of the legs, or collateral circulation superficially in the skin. One gave a history of swelling of both legs 2 months prior to admission which had subsided and remained so after a period of bed rest. Both of these patients were explored transperitoneally with the expectation of transperitoneal nephrectomy. Marked engorgement of the collateral circulation was encountered in each case in the deeper layers of the abdominal wall and within the abdominal cavity. In each case the renal vein and entire inferior vena cava from the renal vein downward were found to be thrombosed and firm. The renal vein in each case was no less than 1 inch in diameter and firmly fixed. In neither case was it felt possible to remove the kidney because of fixation of the growth and the extent of invasion of the vena cava.

Postoperatively it occurred to us that we might have saved both ourselves and the patient a great deal of trouble had we known the true state of affairs before operation. We therefore ran a vena cavogram of each case by the method described by O'Loughlin using 35 per cent diodrast solution injected

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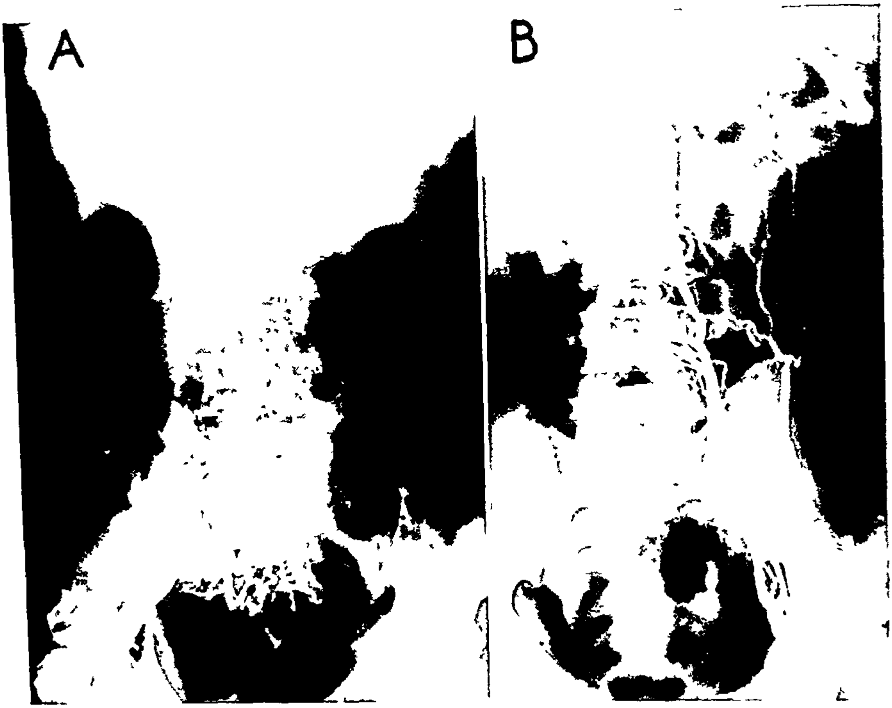

FIG. 1. *A*, injection of right femoral vein showing obstruction in right common iliac region. *B*, injection of left femoral vein showing collateral circulation on left side and no dye in vena cava.

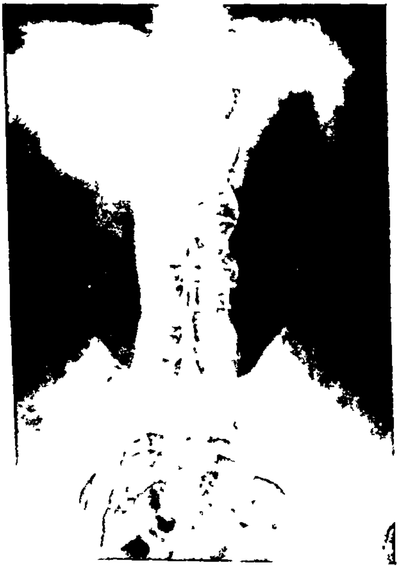

FIG. 2. Normal inferior vena cavogram taken during injection of right femoral vein

rapidly into the femoral vein and exposing a film of the abdomen during the injection. The films obtained are presented in figure 1. Neither patient had any manifestation of ill effect from this procedure. The normal vena cavogram is illustrated in figure 2 and it is obvious that complete obstruction of the inferior vena cava is demonstrable by this method and was present in the 2 cases described.

COMMENT

The findings presented here are offered as evidence that at least extensive involvement of the inferior vena cava in cases of renal neoplasm can be demonstrated by x-ray without undue risk to the patient. The vena cava can be visualized readily with 35 per cent diodrast solution with rapid injection, using the same precautionary tests for sensitivity to the drug as are routinely used for excretory urography. Following the immediate film taken to visualize the vena cava or its collaterals, the routine excretory urograms are easily obtained.

REFERENCES

Hyman, A. and Leiter, H. E.: J. Mt. Sinai Hosp., New York, **4:** 826–839, 1938.
Ney, C.: J. Urol. **55:** 583–590, 1946.
O'Loughlin, B. J.: Am. J. Roentgenol. & Rad. Therapy, **58:** 617–619, 1947.
Pleasants, J. H.: Johns Hopkins Hosp. Rep., **16:** 361–548, 1911.
Simpson, W. M.: Ann. Clin. Med., **3:** 29–68, 1924.

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THROMBO-ANGIITIC OCCLUSION OF THE RENAL ARTERY WITH RESULTANT HYPERTENSION

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The diagnosis and the rational treatment of disease based on correct interpretation of deranged physiologic function are goals which are striven for by practitioners of all branches of medicine and surgery. As a result of the rapid advances being made in laboratory and clinical investigation, it is becoming possible to manage an increasing number of patients in this manner. There remain, however, a great many clinical situations which must still be handled empirically or, at best, with only a partial knowledge of the pathologic physiology responsible for the presenting disease.

Recently, we have had occasion to attend a patient who presented a rare combination of pathologic entities which could be diagnosed, interpreted and treated successfully. Because of its rarity and because it affords clinical verification of certain experimentally proven facts, the following case is reported.

CASE REPORT

Case No. 49-2588. S. P., a 34 year old white Jewish housewife, was admitted to the urologic service of Beth David Hospital June 9, 1949, with a chief complaint of intermittent right lower quadrant pain of 5 days' duration. Approximately three weeks prior to admission the patient experienced, in the right lower quadrant, a sharp pain that persisted for 1 hour and then disappeared spontaneously. She did not consult a physician at that time. Five days before admission, she developed a sharp, steady pain in the right lower quadrant. The pain bore no relation to eating, change of position, urination, or defecation. She vomited 4 times within 24 hours. Seen by a local physician at this time, she was found to have moderate right lower quadrant pain and right costovertebral angle tenderness. The oral temperature was 99.8 F. The physical examination was reported as being otherwise unremarkable. The white blood cells numbered 10,800 cubic mm. with 85 per cent polymorphonuclear neutrophiles, and the urine contained 3 plus albumin but was otherwise without remark. No record of the blood pressure was obtained. A diagnosis of "possible acute appendicitis" was made but was dismissed when the symptoms subsided after 48 hours. During the next 3 days the patient experienced malaise and intermittent right lower quadrant and right flank pain. She was referred to one of us (S. M.) and after a brief examination in the office was admitted to the hospital.

With the exception of the usual childhood diseases the patient had apparently been well until 4 years before the present illness, when she consulted a physician because of cold, pale lower extremities which became painful when she walked a short distance. Her blood pressure at that time was within normal limits. After a complete physical examination, including oscillometric studies, a diagnosis of thrombo-angiitis obliterans was made. The patient was forbidden the use of tobacco (she had previously smoked 30 cigarettes daily) and was treated with vasodilating drugs and exercise of the lower extremities. Despite the admonitions of her physician, however, she continued to smoke 3 to 4 cigarettes daily until the day of admission. Eighteen months prior to admission the patient underwent a normal pregnancy with delivery of a normal infant. Immediately postpartum she was given ergonovine maleate, 0.2 mg., without any apparent ill effects. At no time during the pregnancy or postpartum was any hypertension or albuminuria noted. The remainder of the review of systems was not remarkable. There was no family history of peripheral vascular disease.

On admission the temperature was 98.8 F, pulse 88, respiration 22, blood pressure 190/110. The patient was moderately obese and well developed. She was alert, intelligent and co-operative and did not appear particularly ill. The skin was cool and dry without cyanosis, icterus, eruption or petechiae. Examination of the head was not remarkable. The sclerae and conjunctivae were clear; pupils were round, regular and equal, reacting to light and accommodation. Extra-ocular movements were well performed. The fundi were normal bilaterally. Ears, nose and throat were without remark. The neck was supple and the trachea was in the midline. No tug was present. The thyroid gland was moderately enlarged but no nodules were felt. No generalized or specific lymphadenopathy was detected. Breasts were normal. Lungs were clear to percussion and auscultation and both diaphragms descended equally and well. The heart was not enlarged to percussion; the PMI was within the midclavicular line. The rate was 88, rhythm normal. No murmurs, shocks, thrills, or rubs were noted. Blood pressure was 190/110. The abdomen was soft, the only mass palpable being the spleen, the edge of which could be felt at the left costal margin upon deep inspiration. There was slight tenderness in the right lower quadrant to deep palpation and marked tenderness to a light blow over the right costovertebral angle. Pelvic and rectal examinations were not remarkable. Examination of the extremities revealed absent dorsalis pedis pulsations bilaterally. A popliteal pulsation could be felt weakly on the right but was absent on the left. Femoral pulsations were easily palpable bilaterally. Oscillometric studies revealed absent pulsations at ankle, calf and thigh on the left. The pulsations on the right were markedly diminished but were present at the ankle and calf and were normal in the thigh. On elevation of the feet, the left foot blanched more quickly than the right, and developed rubor more rapidly on dependency. The skin temperature was lower than normal but was equal bilaterally. The radial arteries appeared normal. Neurological examination revealed no sensory or motor abnormalities. The cranial nerves were intact. Tendon jerks were present and equal bilaterally and no abnormal reflexes were elicited.

Laboratories studies: Red blood cells 4.83 million, hemoglobin 14 gm., white blood cells 12,700, polymorphonuclears 84, lymphocytes 9, monocytes 3, eosinophils 4. A catheterized urine specimen was clear and light amber, specific gravity was 1.018, sugar 0, acetone 0, albumin 1 plus, red blood cells 18–20 high power field; white blood cells 25–30/high power field. Urine culture revealed B. coli. The blood urea nitrogen was 17 mg. per cent. The blood creatinine was

1.7, fasting blood sugar 100 mg. per cent. The STS was negative. An electrocardiogram was within normal limits. A flat film of the abdomen revealed a right kidney smaller than normal but was otherwise unremarkable. Excretory urography revealed a normal left pyelo-ureterogram. The right kidney and ureter did not visualize (fig. 1, *A*). Cystoscopy demonstrated a normal fundus and bladder. Both ureteral orifices were normal in size, shape, position and appearance. A few cubic centimeters of urine were obtained from the right kidney after ½ hour. This urine contained 4 plus albumin. After an intravenous injection of indigo carmine, the dye spurted from the left ureteral orifice in heavy concentration within 3 minutes. No dye was seen to emerge from the right ureteral orifice over a period of 30 minutes. Retrograde pyelography demonstrated a normal right retrograde pyelo-ureterogram in a small right kidney (fig. 1, *B*).

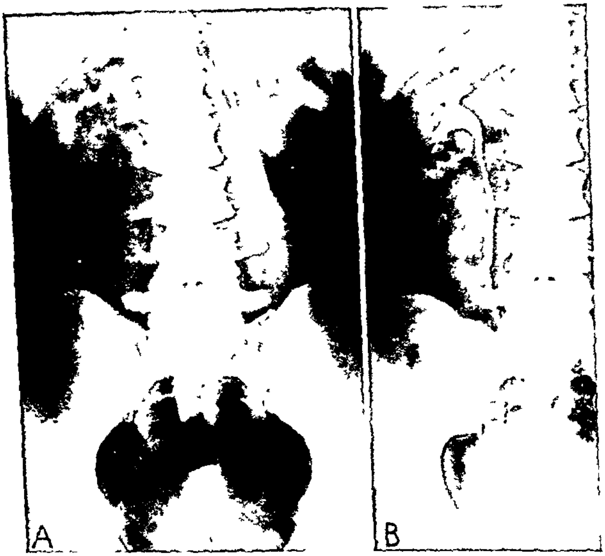

Fig. 1

The day following admission the patient's blood pressure rose to 230/130. The right flank pain continued and gradually grew more severe, requiring opiates for relief. She was given benzazoline (Priscol Ciba) 50 mg. every 6 hours, without effect. On the second hospital day she was placed on anticoagulant therapy. On the third hospital day, a right splanchnic plexus block with 40 cc of 1 per cent procaine produced some relief of the right lower quadrant pain. The blood pressure continued to rise and on the fifth hospital day was 240/130 in the recumbent position bilaterally. She developed an agonizingly severe, constant, right occipital headache. Since the patient was obviously pursuing a rapidly downhill course, surgical intervention for relief of the hypertension was decided upon.

Based upon 1) the history of thrombo-angiitis obliterans, 2) nonvisualization of the right kidney by excretory urography, 3) a normal right retrograde pyelogram and 4) fulminating hypertension, the preoperative diagnosis was thrombosis of the right renal artery with right renal ischemia and resultant hypertension. The anticoagulent therapy was discontinued; she was given vitamin K parenterally and, on the sixth hospital day, an operation was performed by one of us (S. M.).

Under cyclopropane anesthesia a right oblique lumbar incision was made and the right kidney exposed. The kidney was about one half its normal size but was otherwise unremarkable in appearance and consistency. Palpation of the renal pedicle revealed the main renal artery to be pencil-hard in consistency and about 1.5 cm. in diameter. The renal vein appeared to be grossly normal. There were several moderately large aberrant arteries and veins entering and leaving the kidney. A right nephrectomy was performed without difficulty and the patient left the operating room in good condition. Shortly after ligation of the renal pedicle, the arterial tension, which had been 240/140 at the beginning of the surgical procedure, dropped to 125/70, and 4 hours later the pressure dropped to 72/30. She was then given an intravenous infusion of 500 cc plasma and later during the day 1000 cc of 5 per cent glucose in normal saline to combat secondary peripheral vascular collapse. She rallied in short order and the blood pressure stabilized at approximately 120/70 that evening. She was made ambulatory on the second postoperative day and, after an uneventful recovery, was discharged on the sixteenth hospital day. At the time of discharge her blood pressure was 130/70 and urinalysis was completely normal. Following discharge from the hospital the patient did very well, although she continued to experience intermittent claudication. Examination 12 months postoperatively revealed that the blood pressure was 114/72 in the right arm and 112/68 in the left arm in the recumbent position. Her peripheral vascular status was unchanged. The operative scar was well healed and the patient had no complaints other than those referable to her lower extremities. The blood urea nitrogen was 15 mg. per cent and urinalysis was not remarkable.

Pathological report: The gross specimen consisted of a kidney measuring 7.5 by 4 cm. in diameter, and weighing 55 gm. The capsule stripped with ease revealing a reddish-brown surface on section. The cortex was markedly narrowed and measured 2 to 3 mm. in width. The cortex and medulla were well demarcated. The cortex was yellowish-brown in color. The medulla was dark red. The renal pelvis was smooth. The ureter measured 2 cm. in length and was narrow. The renal artery was markedly thickened and firm; cross section revealed a thrombus which was reddish-brown in color. The wall of the artery was markedly thickened, firm and yellowish-grey in color. The renal vein was of normal size; its wall was narrow and the lumen patent.

Microscopic examination (fig. 2) of the renal artery revealed changes typical of thrombo-angiitis obliterans. The lumen was markedly narrowed by a fibrous proliferation between the muscle fibers of the media disrupting the normal architecture. The internal elastica was hypertrophied and thickened. The external elastica was also hypertrophied and degenerated and the adventitia was considerably thickened by an increase in collagenous tissue. The adventitia showed slight residual inflammatory cell infiltration. There were many hypertrophied sympathetic nerves in the thickened periadventitial connective tissue. The small lumen of the artery contained some recent thrombotic material, although the occlusive process obviously had been a gradual one. Some of the smaller arterial branches outside the adventitia showed thickening of the media and occlusion of the narrowed lumina by thrombotic material.

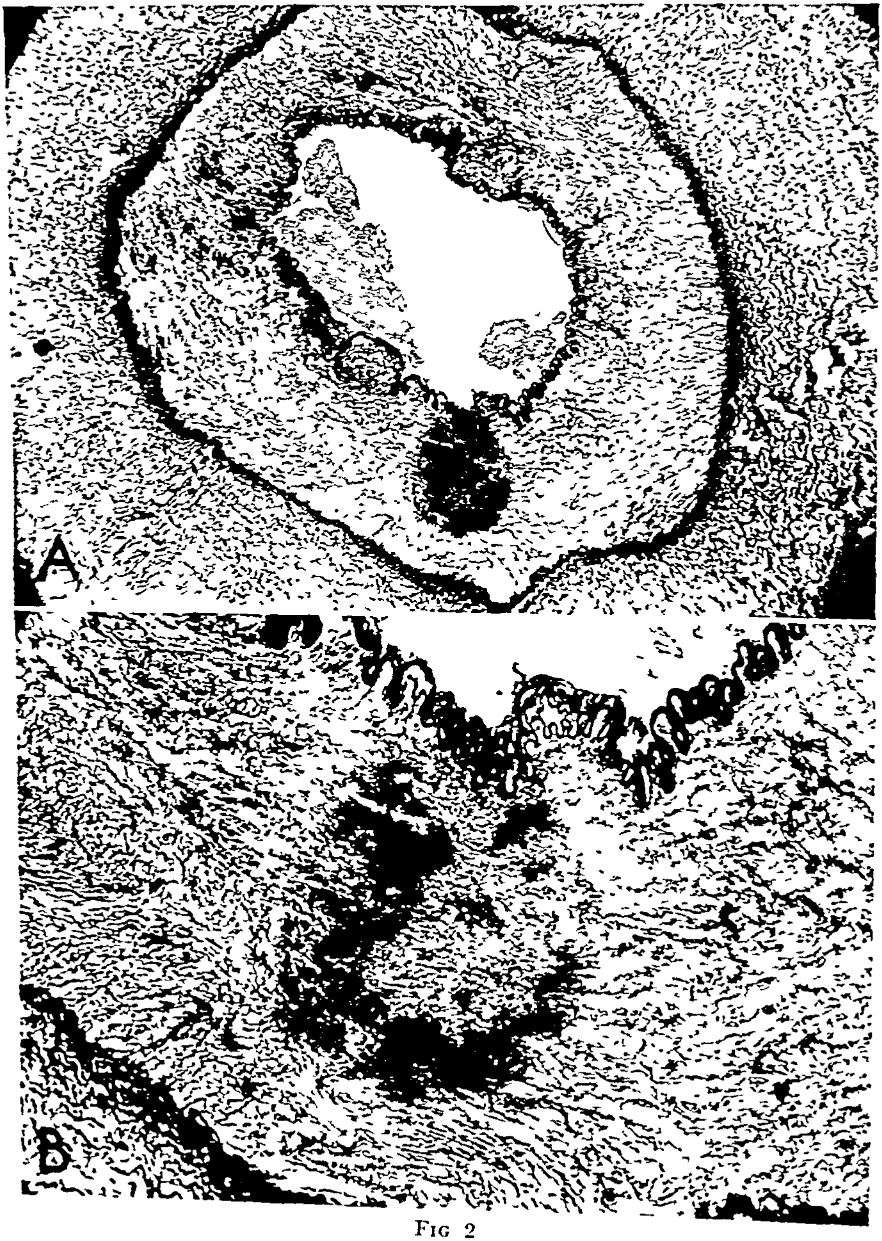

Fig 2

The renal vein exhibited slight fibrous thickening of the intima and hypertrophy of the muscular elements in the media

Sections of the kidney revealed intimal fibrosis and thickening with variable luminal narrowing. There were areas of degeneration and necrosis in the papillae, fresh interstitial medullary and cortical hemorrhages, degeneration of the epithelium of the convoluted tubules including the loops of Henle as well as of the collecting tubules, and casts containing some leukocytes and red cells in the tubular lumina. There was also some interstitial fibrosis. The glomeruli were congested but otherwise the capsules and tufts were very well preserved. Only a few hyalinized, atrophied glomeruli were found. There was some patchy interstitial inflammatory round cell infiltration.

COMMENT

Renal artery thrombosis is not synonymous with renal infarction, which is frequently due to venous thrombosis on the basis of inflammatory or traumatic lesions involving the renal veins (Goodyear and Beard, 1947; Abeshouse, 1945). Obstructive lesions of the main renal artery may be divided into extrinsic and intrinsic types (Yuile, 1944). Among the various etiologic factors which may be involved in the production of this condition are: neoplastic disease, infection, trauma, embolic phenomena, thrombosis in situ, and intrinsic obliterative disease of the vessel itself. In this paper we are concerned primarily with the last two categories.

Embolism of the renal artery, which is the commonest cause of occlusion of this vessel, is frequently confused with thrombosis in situ, but, although the end results may be similar, the underlying disease processes are quite different. The diagnosis of embolism of the renal artery is not usually a particularly difficult one, since in most cases the source of the embolus can be readily determined. Thus, a careful cardiologic examination will usually reveal auricular fibrillation, vegetative endocarditis, evidence of mural thrombi, or some other obvious lesion to account for arterial occlusion at the distant site.

Unfortunately, thrombosis of the main renal artery is rarely diagnosed antemortem, despite the fact that such a conclusion can be arrived at logically if the examining physician bears the possibility in mind. The diagnosis may be made on the basis of 1) careful history taking, with particular reference to the cardiovascular system, 2) a complete physical examination, 3) a thorough survey of the urinary tract, including excretory and retrograde urography, and 4) salient laboratory findings. These diagnostic criteria have been excellently reviewed by Wolffe (1943) who reviewed 27 cases, and by Goodyear and Beard (1944).

Urologic examination with ureteral catheterization and pyelography in cases of complete occlusion of the renal artery reveals an absence of urine on the involved side, failure of indigo carmine excretion, and nonvisualization of the kidney in an excretory urogram. Retrograde pyelography, however, fails to reveal any abnormalities because of the fact that, with the exception of long-standing cases accompanied by destruction, the pelvis and calyces are not involved by this condition.

In theory, the disease presenting the greatest difficulty in differential diagnosis is thrombosis of the renal vein. Several findings, however, serve to distinguish the two conditions. Venous thrombosis of the kidney has a lower age incidence, approximately 40 per cent of the cases occurring in children less than 1 year of age. Thrombosis of the renal artery is primarily a disease of adult life and is most commonly seen during the years when generalized atherosclerosis manifests itself. In patients with thrombosis of the renal vein, arterial disease elsewhere in the body is usually absent. If arterial disease is present, it is coincidental except in cases of thrombo-angiitis obliterans, periarteritis or obliterative endarteritis. Hypertension is less common in venous thrombosis than in arterial thrombosis. Finally, retrograde pyelography in cases of thrombosis of the renal vein reveals either an irregular outline and incomplete filling of the pelvis or complete failure of the pelvis to fill. As mentioned previously, thrombosis of the renal artery usually fails to demonstrate any abnormalities in the retrograde pyelogram. For a full discussion of thrombosis of the renal veins, the reader is referred to the masterful review of the subject by Abeshouse (1945).

Although the vast majority of thromboses in situ occurring in the renal artery are localized manifestations of generalized atherosclerotic disease, other intrinsic disease of the arteries may act as the primary etiologic agent. Thrombo-angiitis obliterans, which was originally thought to be an almost purely peripheral vascular disease, is now recognized as a pathologic process which very frequently affects the vessels supplying and draining the viscera. Among the numerous reports in the literature indicating involvement of practically all vessels of the body by thromboangiitis obliterans are the following: Jaeger, 1932; Sprunt, 1934; Eppinger, 1936; Perla, 1925; Livingston, 1933; Eisendrath, 1934; Podoba, 1947.

It is only to be expected, therefore, that a certain proportion of patients with Buerger's disease will have lesions of the renal vessels. Sprunt (1934), in a review of all autopsies on cases of thrombo-angiitis obliterans reported in the literature up to 1934 (a total of 18 cases), states that one or both renal arteries were involved in 8 cases. A careful review of the original case reports, however, indicates that 4 of these cases (Perla, 1925; Nordmann and Van Reuyes, 1931; Ackman, 1931; Livingston, 1933) either did not have thrombo-angiitis obliterans or the thrombo-angiitis obliterans did not involve the renal arteries. There is no doubt in our minds, however, that the renal vessels are affected more commonly than the literature indicates. Eisendrath (1934) reports a case of thrombosis of the main renal vein in a 30 year old man with thrombo-angiitis obliterans. Podoba (1947) has recorded the only case in the literature similar to our own. His patient was a 36 year old man with thrombo-angiitis obliterans of 7 years' duration. He developed a permanent hypertension of 200 140 several years before death occurred from cardiac insufficiency. At autopsy he was found to have thrombo-angiitis obliterans of the coronary arteries and the abdominal aorta, with stenosis of both renal arteries. Podoba felt that the hypertension was caused by ischemia of both kidneys due to thrombo-arteritic stenosis of both the arteries.

Thrombo-angiitis obliterans was originally thought to be confined almost exclusively to Jewish males of Russian descent. This concept, however, has long since been revised. The disease occurs in Gentiles as well as Jews and, although the incidence among males is far higher than in females, evidence is available that it is becoming more prevalent among the latter sex. Silbert (1948) estimates that 4 per cent of all cases of thrombo-angiitis obliterans now occur in women.

whereas 25 years ago the incidence was only 1 per cent. He attributes the change to the fact that the use of tobacco by women has greatly increased during this period. It is interesting that there is a higher incidence of cerebral thrombo-angiitis obliterans (3 per cent) among women with the disease than in men (1 per cent). This may well indicate that generalized visceral thrombo-angiitis obliterans is more common among women with this vascular disease.

The relationship between hypertension and renal disease, first elucidated by the fundamental work of Goldblatt in 1933, and recently reviewed by him (Goldblatt, 1948), is too well known to warrant a lengthy discussion here. Suffice it to say, that high blood pressure caused by unilateral renal disease is one of the few forms of hypertension which can, on occasion, be completely cured at the present time. Such cures have been reported by numerous authors and we personally have published one such case (Malisoff, Light, and Macht, 1941). Unilateral renal ischemia with resultant hypertension may be caused by a great variety of pathologic processes, among which is thrombosis of the renal artery. An illustrative case if that of Shea, Schwartz, and Kobilak (1948). Their patient, a 33 year old white man, was hospitalized for hypertension of 205/125. Urologic examination demonstrated a small, poorly functioning left kidney and a normal right kidney. A left nephrectomy was performed and within 8 hours the blood pressure returned to normal limits, where it remained. Pathologic examination revealed an organized thrombus partially occluding the left renal artery.

Insofar as we can determine, ours is the first reported case of thrombo-angiitis obliterans in a woman causing occlusion of one renal artery with resultant hypertension. The case is particularly rare because of 1) the low incidence of thrombo-angiitis obliterans in females, 2) the rarity of renal hypertension as a result of this disease, and 3) the preoperative diagnosis with surgical cure of the hypertension. It is instructive in that it illustrates the possibility of a diagnosis and treatment of this condition on the basis of a correct interpretation of deranged physiologic function. The case may be summarized diagramatically as follows:

30 year old white woman with thrombo-angiitis obliterans of peripheral vessels
↓ 4 years
Visceral involvement by thromboangiitis obliterans
with occlusion of right renal artery at age 34
↓
Unilateral renal ischemia
↓ 21 days
Fulminating hypertension
↓
Right nephrectomy
↓
Normal arterial tension

SUMMARY

The pathogenesis and clinical features of renal artery occlusion, with particular reference to thrombo-angiitic involvement of the renal vessels, are discussed.

A case of a 34 year old white woman with hypertension caused by thrombo-angiitic occlusion of the right renal artery, diagnosed preoperatively and successfully treated surgically, is presented. This is the first such case to be reported in the literature.

The pertinent literature is briefly reviewed and the derangement of physiologic function in the authors' case is discussed.

REFERENCES

Abeshouse, B. S.: Urol. & Cutan. Rev., **49:** 661, 1945.
Ackman, F. D.: Can. Med. Assoc. J., **25:** 657, 1931.
Eisendrath, D. N.: J. d'urol., **37:** 47, 1934.
Eppinger, E. C.: Thromboangiitis obliterans. A case with extensive distribution of the vascular lesions including the coronary arteries. In Medical Papers Dedicated to Henry A. Christian. Waverly Press, Baltimore, 1936.
Goldblatt, H.: The Renal Origin of Hypertension. Springfield, Ill.: Charles C. Thomas, 1948.
Goodyear, W. E. and Beard, D. E.: New Eng. J. Med., **237:** 355, 1947.
Jaeger, E.: Virchow's Arch. f. path. Anat., **284:** 526, 1932.
Livingston, W. K.: West. J. Surg. Obst. Gyn., **41:** 21, 1933.
Malisoff, S., Light, I. and Macht, M. B.: J. Urol., **46:** 209, 1941.
Perla, D.: Surg. Gynec. & Obst., **41:** 21, 1925.
Podoba, J. Z.: Casopsis Lekaru Ceskych, Prague, **86:** 548, 1947.
Silbert, S.: Am. Heart J., **36:** 757, 1948.
Shea, J. D., Schwartz, J. W. and Kobilak, R. E.: J. Urol., **59:** 302, 1948.
Sprunt, T. R.: South. Med. J., **27:** 698, 1934.
Wolffe, J. B.: Urol. & Cutan. Rev., **47:** 276, 1943.
Yuile, C. L.: Obstructive lesion of the main renal artery in relation to hypertension. Am. J. Med. Sci., **207:** 394, 1944.

Additional References

Aschner, P. W.: Am. J. Med. Sc., **164:** 386, 1922.
Barney, J. D.: New Eng. J. Med., **207:** 817, 1932.
Brown, C. E., Allen, E. V. and Mahorner, H. R.: Thromboangiitis Obliterans. Philadelphia: W. B. Saunders Co., 1928.
Buerger, L.: The Circulatory Disturbances of the Extremities. Philadelphia: W. B. Saunders Co., 1924.
Dalrymple, S. C.: New Eng. J. Med., **203:** 160, 1930.
Danheiz P.: J. d'urol., **23:** 481, 1927.
Desjacques, R. and Boijeau, A.: Lyon chir., **33:** 645, 1936.
Fikentscher, R.: Multiple Infarcts in the Kidneys in Endarteritis Leutica Obliterans. Inaugural Dissertation, pp 1–48, 1928.
Lemierre, A.: Prat. Med. Franc., **13:** 711, 1932.
Makai, A.: Zentralbl f. Chir., **53:** 2977, 1926.
McKenna, C. M.: Trans. Am. Assoc. Genito-Urin. Surg., **20:** 203–212, 1927.
Metzler, F : Ztschr. f. Urol **22:** 106, 1928.
Moschowitz, E.: Proc. N. Y. Path. Soc , **5:** 81, 1905–1906.
Pontieri, F.. La Pediatria, **44:** 159, 1936
Schildt, E · Acta Chir. Scandinav., **70:** 299, 1933.
Schmidt, R.: Wein. klin. Wchnschr. **14:** 451 and 486, 1901.
Staehler, W : Bruns' Beitrage zur klin. Chir. **167:** 189, 1938.
Vogelsand, A. D.· Ohio State Med. J., **36:** 269, 1940.
Von Adler-Racz, A · Ztschr f Urol., **27:** 40, 1933.
Weiss, F · Ztschr f. med , **120:** 199, 1932.

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LYMPHOBLASTOMATOUS NEPHROPATHY

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Involvement of the urinary tract by lymphoblastomas is of statistical significance. According to Watson, Sauer and Sadugor,[1] in a study of 1073 cases of lymphoblastoma, there were symptoms referable to the genito-urinary tract in 7.5 per cent, a total of 80 cases. Upon histological examination of 143 autopsies, however, there was involvement of the urinary tract in 62 cases or 44 per cent. The kidney is the predominant organ affected.

Pathological changes in the kidney may be of three types:[2] nodular, diffusely infiltrative; and, rarely, masses at the hilus which resemble leukemic marrow. This third type is noninvasive, is thought by some to represent extramedullary hematopoiesis in hilar fat, and may cause ureteropelvic junction obstruction.[3] Primary lymphosarcoma of the kidney is said never to occur.[4]

Clinical findings due to secondary involvement of the upper urinary tract by metastasis, or direct invasion of the lymphatics surrounding the ureter or renal hilus causing compression, ordinarily simulate either renal colic from constriction of the ureter by retroperitoneal lymphoma or primary renal neoplasm.[5] Chute[6] has cited a case of obstruction of both ureters by retroperitoneal lymphoma with a resulting hydronephrosis. A report has been made by the Massachusetts General Hospital[7] of a patient with a large retroperitoneal lymphomatous mass in the posterior root of the mesentery surrounding the vena cava and both ureters close to their junction with the pelves. This patient had acute suppression of urine for seven days prior to death. An autopsy protocol of a similar instance has been reported by Flashman.[8] Barney, Hunter and Mintz[9] have cited a case of a 9 year old boy with myelogenous leukemia and involvement of the retroperitoneal and mesenteric glands which caused ureteral obstruction. Two unusual cases of compression of the ureters have been reported by Ormond.[10] These are distinctive in that envelopment was by nonmalignant inflammatory tissue and scar tissue which occupied the greater part of the retroperitoneal space. A retroperitoneal lymphoblastoma simulating a primary kidney neoplasm has been reported by Mathé.[11] Three instances of lymphosarcomatous replacement of the kidney have been cited.[12, 13] Because of the difficulties in differ-

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Hot Springs, Va., March 24, 1950.

[1] Watson, E. M., Sauer, H. R. and Sadugor, M. G.: J. Urol., **61:** 626, 1949.

[2] Meyer, L. M.: Urol. and Cut. Rev., **45:** 693, 1941.

[3] Weber, F. P.: Quart. J. Med., **12:** 122, 1919.

[4] Miller, C. O.: J. Urol., **62:** 439, 1949.

[5] Gibson, T. E.: J. Urol., **60:** 838, 1948.

[6] Chute, R.: J.A.M.A., **97:** 969, 1931.

[7] New Eng. J. Med., **202:** 1215–1218, 1930.

[8] Flashman, D. H. and Leopold, S. S.: Am. J. M. Sc., **177:** 651, 1929.

[9] Barney, J. D., Hunter, F. T. and Mintz, E. R.: J. A. M. A., **98:** 1215, 1932.

[10] Ormond, J. K.: J. Urol., **59:** 1072, 1948.

[11] Mathé, C. P.: J. Urol., **17:** 357, 1927.

[12] Pease, G. L. and McDonald, J. R.: Am. J. Clin. Path., **17:** 181, 1947.

[13] Paul, M.: Urol. and Cut. Rev., **44:** 751, 1940.

ential diagnosis and of the possibility of the favorable response of this group of cases to radiation therapy, the subject of lymphoblastomatous nephropathy should be of great interest to the urologist. The following case is presented as a significant addition to this category.

CASE REPORT

A well nourished 45 year old white married man was referred to Dr. Shivers by Dr. James H. Mason on March 29, 1948 because of swelling of the skin of the penis and scrotum. This was first noticed by the patient at 1 a.m. on the day that he consulted his physician. He had no urinary symptoms, but complained of pain in the small of the back radiating anteriorly to the right side. The patient denied having had gonorrhea or syphilis. Malaria was contracted 18 years ago with no recurrent attacks. There was no history of urinary tract disease. The pain in the back, which the patient stated was never of sufficient severity to cause him to seek medical aid, was first noticed following a cold one month previously. At 17 years of age, fatty tumors were removed from the right upper abdomen. (We were unable to obtain a report on the pathological findings.) The family history was unimportant.

Examination of the external genitalia showed moderate edema of the shaft of the penis and prepuce. On the right side of the prepucial skin surface was a moderate size wart. No ulceration or abrasion was found on the skin of the glans or undersurface of the prepuce. A uniform edema of the scrotal tissues was noted. The spermatic cords, epididymides and testicles were normal. No abrasion of the skin of the scrotum was present. Slight edema of the skin in the pubic region was present; both thighs were negative. No urethral stricture was found. The inguinal and femoral glands were slightly enlarged, more so on the right. The glands in the right groin were more tender than those on the left.

The abdomen was flat. A tympanitic note was elicited above the symphysis with no pain on pressure. There was some involuntary rigidity of the abdominal muscles. It was noted that the patient was extremely nervous and difficult to examine. An irregular scar was present in the upper right abdomen. The liver was not enlarged. The kidneys were not palpable. No tenderness was elicited on fist percussion at either costovertebral angle.

Rectal examination of the prostate and seminal vesicles revealed an elastic and movable gland of normal size with a depressed center. The base of the bladder was normal. The seminal vesicles were not palpable.

The patient was admitted to the Atlantic City Hospital 2 days later for a more complete study. An excretory urogram showed a right hydronephrosis in the 1 hour film with no dye in the left renal pelvis at the end of 2 hours. The intake and output chart showed a progressive diminution in the output of urine until 7 days after admission when the output dropped abruptly to 8 ounces in 24 hours with a corresponding rise in the blood urea nitrogen. Cystoscopy at this time showed a normal bladder. Indigo carmine failed to appear from either orifice in 7 minutes. A 5F catheter was passed up the right ureter 32 cm. after temporarily meeting obstruction at 25 cm. Sixty-four cubic centimeters of clear water-colored urine were withdrawn from the right renal pelvis with only a trace of the dye noted in the specimen. Smears and cultures obtained from the bladder and right kidney urines were negative.

The catheter was left inlying for several days, at the end of which time it was withdrawn. There was a marked decrease in the daily output of urine following its removal (fig. 1, *A*). A second cystoscopy was done within a few days, at which time 6F catheters were passed to the renal pelves with ease. Only a very scant output of urine came from the left kidney with a marked hydronephrotic drip from the right. A divided phenolsulfonphthalein test showed 10 per cent excretion by the right kidney in 20 minutes and no measurable function from the left. Smear and culture revealed Bacillus coli in the urine of both kidneys. The 20 minute delayed upright film disclosed right hydronephrosis and hydroureter with evidence of obstruction of the ureter at the level of the upper border of the fourth lumbar vertebra (fig. 1, *B*). The patient was maintained on bilateral ureteral catheter drainage for a period of 3 weeks in an attempt to improve kidney function and for further dilatation of the ureters. A divided phenolsulfonphthalein test at the end of that time revealed 50 per cent excretion by the right kidney in 1 hour with no dye appearing from the left. The blood urea nitrogen was 33 mg. per cent in contrast to 112 mg. per cent on admission.

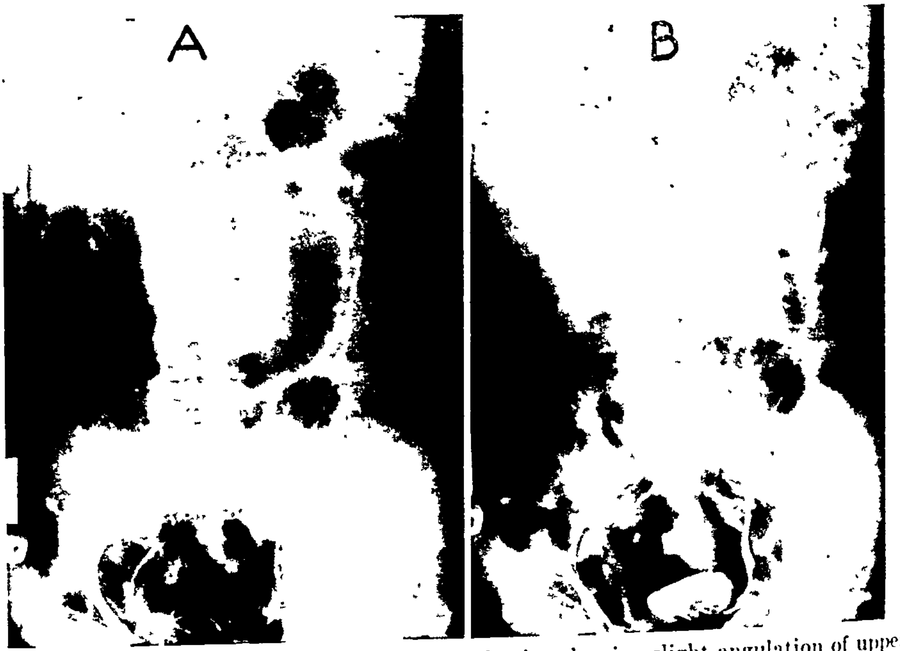

FIG. 1. *A*, plain film with ureteral catheters in situ showing slight angulation of upper third of left catheter. *B*, right pyelo-ureterogram: Delayed 20 minute upright film showing evidence of retention and location of obstruction.

No left pyelogram was made because on every examination the left kidney was functionless and we believed that the poor general condition of the patient did not warrant detailed examination of a kidney which was beyond salvage, although it would have been of interest in reporting this case. We assume that the involvement of the left urinary tract was much more extensive than the right and probably occurred earlier as the kidney was functionless on the first examination. It might be noted further that the patient never complained of any pain or discomfort in the left lumbar region.

From the clinical findings, the functionless left kidney, the appearance of the right pyelo-ureterogram and the fact that no permanent improvement resulted from ureteral dilatation, we came to the conclusion that we were dealing with extrinsic pressure probably involving both ureters and a tentative diagnosis of lymphoblastomatous involvement of the urinary tract was made. We decided to expose the right or functioning kidney and its ureter, and, if we were correct, to establish more adequate drainage by nephrostomy. At operation, the kidney was found to be of normal size with no evidence of hilar involvement. The right ureter, at the level of the fourth lumbar vertebra, was compressed by multiple, hard, discrete lymph nodes. Similar nodules were noted to be scattered throughout the retroperitoneal area. Because of the nature of the obstruction and the suspicion that we were dealing with some form of lymphoblastoma, a nephrostomy was done.

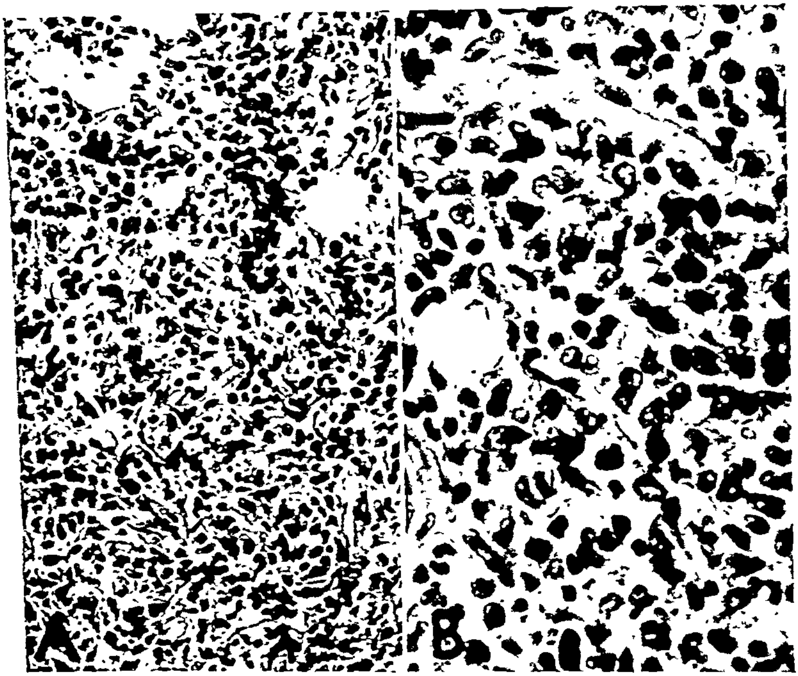

FIG. 2. *A*, lymph node. Reticulum cell sarcoma. Low power photomicrograph showing cellular area with coarse reticulum. X 200 (H. and E. stain). *B*, lymph node. Reticulum cell sarcoma. High power photomicrograph showing cellular detail. Pleomorphism, coarse nuclear markings. X 440 (H. and E. stain).

Histological examination of the removed tissue with H. & E. and Silver stains disclosed a dense fibrous stroma through which coursed a reticulum. In the spaces water-colored urine were withdrawn from the right renal pelvis with only a trace of the dye noted in the specimen. Smears and cultures obtained from the bladder and right kidney urines were negative.

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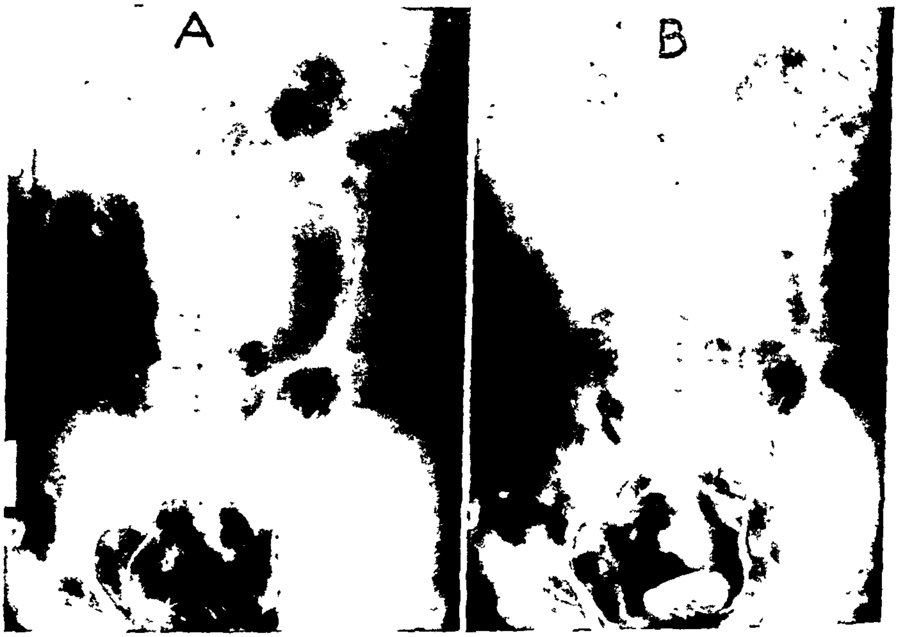

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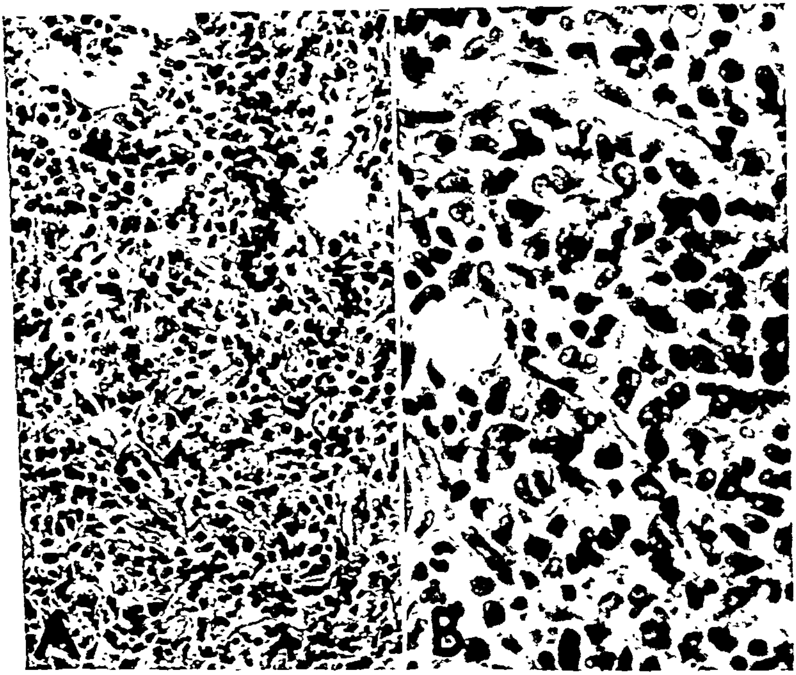

FIG. 2. *A*, lymph node. Reticulum cell sarcoma. Low power photomicrograph showing cellular area with coarse reticulum. × 200 (H. and E. stain). *B*, lymph node. Reticulum cell sarcoma. High power photomicrograph showing cellular detail. Pleomorphism, coarse nuclear markings. × 440 (H. and E. stain).

Histological examination of the removed tissue with H. & E. and Silver stains disclosed a dense fibrous stroma through which coursed a reticulum. In the spaces of the reticulum and also adhering to the fibers there were reticulum cells. These possessed an oval, sometimes kidney shaped nucleus, rather delicate markings and a small nucleolus. In some places the reticulum cells were closely packed and such details were not discernible. Here and there were large immature reticulum cells with a more coarsely marked nucleus and with an occasional cell revealing a large nucleolus. Therefore a diagnosis of reticulum cell sarcoma was made. See figure 2.

A course of x-ray therapy was instituted 12 days after the operation. A total of 1300 air r. were delivered to each of two retroperitoneal ports in 5 sittings during a one week period. The response was remarkable and the patient was able to leave the hospital 19 days following the operation with instructions to return for further radiation. The patient, however, failed to report for this treatment. His improvement persisted for a period of 2 months, at the end of which time he began to lose weight rapidly and was re-admitted for a course of nitrogen mustard therapy. The admitting resident noted a generalized lymphadenopathy, anemia, cachexia and a weight of only 88 pounds. The blood urea nitrogen remained 30 mg. per cent. Drainage was satisfactory through the nephrostomy tube. A transfusion of 1000 cc of blood was given for his anemia. The patient then received 4 mg. of nitrogen mustard on four consecutive days. Nausea, vomiting and diarrhea followed each dose. At the request of the family, the patient was sent home September 2, 1948. His course was rapidly downhill and he died 5 weeks following discharge.

DISCUSSION

It was unfortunate that the patient died outside of the hospital, as we were unable to obtain an autopsy which would have been of interest in ruling out direct invasion of the urinary organs. At operation there was no gross evidence of involvement of the right kidney by tumor. The obstruction to the ureter was entirely extrinsic resulting from pressure of the involved lymph nodes. The ureter proximal to the point of obstruction was greatly dilated.

It must be admitted that we were at a loss to explain the symptoms which the patient presented at the time he was first examined because he appeared to be in such excellent health and had been working daily as a taxicab driver. The slight backache he complained of, which was not of sufficient severity to cause him to consult a physician, is not an uncommon finding in an individual with this type of occupation. The patient was concerned principally with the sudden appearance of edema of the skin of the scrotum and shaft of the penis and it was this finding which prompted him to consult his physician. Although the inguinal and femoral glands were palpable, there was no undue enlargement. Later on, the glandular involvement was much more pronounced.

After a complete study, we were cognizant of the fact that in addition to lymphatic obstruction causing edema of the skin of the scrotum, penis and lower abdomen, with some enlargement of the inguinal glands, we were dealing with ureteral obstruction which appeared to be extrinsic. As a result of this obstruction, we found a functionless left kidney with a right hydronephrosis and dilatation of the upper portion of the ureter with no apparent displacement of the kidney.

The literature on lymphoblastomatous involvement of the urinary tract suggests that postmortem examination shows it to be a common finding. However, it must be remembered that the clinical manifestations produced by these changes are comparatively infrequent, but if one will keep the possibility in mind in cases of extrinsic ureteral obstruction, fewer mistakes will be made.

We realize that surgery in lymphoblastomatous disease is generally ill-advised. However, there are certain indications for more adequate renal drainage than can be obtained by ureteral catheters. Some type of drainage was a must in our case as each time the right ureteral catheter was removed, a marked drop occurred in the urinary output, and a corresponding rise in the blood urea nitrogen. Our results from radiation, except in the early stage of the treatment, and nitrogen mustard therapy were generally unsatisfactory. However, the total amount of radiation that our patient received was entirely inadequate, and we believe that his life could have been lengthened considerably had he been willing to submit to a sufficient amount of x-ray therapy. Unquestionably the nephrostomy drainage aided in the temporary recovery of the patient and maintained good renal function until death.

SUMMARY

The literature concerning lymphoblastomatous nephropathy has been reviewed.

The authors have presented an additional significant case emphasizing the diagnostic difficulties encountered and the therapeutic aids employed.

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CUTANEOUS METASTASES FROM TRANSITIONAL CELL CARCINOMA OF THE RENAL PELVIS AND BLADDER

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Cutaneous metastases from transitional cell carcinoma are rare. The literature contains little discussion on such metastases and most writers report metastastic lesions from carcinoma of the bladder to the bones, abdominal viscera, brain, and lungs. The Committee on Carcinoma Registry listed only 2 of a series of 902 epithelial tumors of the urinary bladder as having skin metastasis. Higgins and Hausfeld found in the literature 8 cases of carcinoma of the urinary bladder with cutaneous metastases and reported 2 cases. They further mention that in personal communications with urologists, many replied that they had seen one or more cases of carcinoma of the bladder with skin metastases. This has also been borne out in our experience. These authors have made a plea for publication of such cases in order that a more accurate evaluation of transitional cell carcinoma may be made.

This case report is in response to that plea. It is of particular interest because of the progressive spread of an initial papillary carcinoma of the renal pelvis to the bladder and prevesical space with ultimately the distant metastases in the skin and elsewhere.

CASE REPORT

A 50 year old white man was admitted to Brooke General Hospital with painless hematuria which had occurred in several transient episodes during the preceding 9 months. Pyelographic studies revealed a marked filling defect of the left renal pelvis. On August 9, 1945, nephro-ureterectomy was performed. Microscopic examination of sections of the kidney and ureter showed the presence of a papillary transitional cell carcinoma limited to the renal pelvis (fig. 1, *A*). Convalescence was uneventful following operation and the patient was subjectively well for 1 year, when hematuria again appeared. He was re-admitted to Brooke General Hospital and extensive metatastic bladder lesions were treated by suprapubic excision and fulguration. Microscopic examination of these bladder lesions showed them to be transitional cell papillary carcinoma, grade 2 (fig. 1, *B*). The convalescence was uncomplicated. From that time until his final admission, recurring papillary carcinomatous lesions in the bladder were treated by transurethral excision and fulguration, at intervals not exceeding 3 months. In January 1948, a suprapubic prevesical mass developed; it was excised and found to be a local recurrence of transitional cell carcinoma in subcutaneous tissue (fig. 1, *C*). The ovoid, encapsulated gross specimen measured 8 by 5 cm. In November 1948, thirty-nine months following removal of the left kidney, a cutaneous lesion over the right side of the forehead was present. It was grayish-yellow in color with verrucous surface, and measured 13 by 13 by

5 mm. The lesion was excised and the defect was covered with a full thickness skin graft. Microscopic examination showed this lesion to be metastatic transitional cell carcinoma, the microscopic appearance of which was essentially iden-

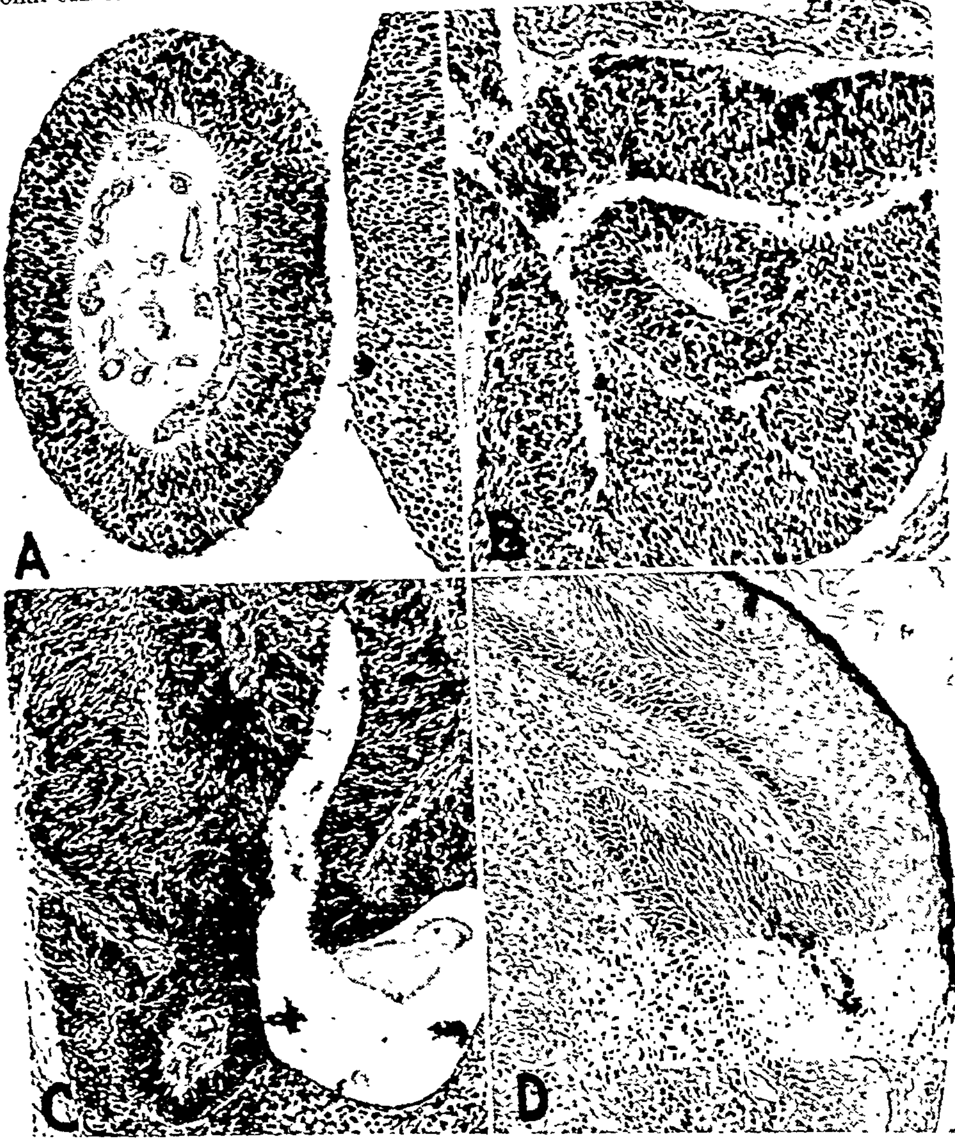

Fig. 1. *A*, papillary transitional cell carcinoma of left renal pelvis. *B*, secondary papillary transitional cell carcinoma of bladder. *C*, metastatic papillary transitional cell carcinoma in prevesical space. *D*, cutaneous metastasis of transitional cell carcinoma to forehead. × 105.

tical with that seen in the previously described lesions of the renal pelvis, bladder and vesical space (fig. 1, *D*). During the next 5 months the patient's course was gradually downhill, and widespread metastases became evident in the lungs and bones including involvement of the left clavicle with a pathological fracture. In addition, 4 cutaneous nodules appeared in the scalp. Emaciation became extreme and the patient died on May 6, 1949.

Autopsy revealed transitional papillary carcinoma of the urinary tract with metastases to the inguinal and aortic lymph nodes, lungs, bladder, seminal vesicles, left clavicle, ribs, pubis, and lumbar vertebra. In addition there were *metastases to the subcutaneous tissues of the lower abdomen and cutaneous* metastases in the scalp.

DISCUSSION

It is most unusual to see such widespread and diffuse metastases from transitional cell carcinoma of the urinary tract. Although the exact mechanism effective in producing cutaneous metastases is not known, it is considered that such metastases are the result of blood borne neoplastic cells, with eventual penetration into the lymphatics of the skin. The sequence of spread in this case of primary transitional cell papillary carcinoma of the renal pelvis appears to have been by direct implantation into the bladder, with seeding of the prevesical space at the time of suprapubic excision of the secondary vesical lesions, followed, after a considerable interval, by cutaneous metastases to the forehead and scalp. It is interesting that microscopic appearance of the cutaneous metastases to the forehead was unequivocally identifiable with those from the renal pelvis, bladder and prevesical space. Once lymphatic penetration of the skin has occurred it is easily understandable how diffuse cutaneous metastases could occur as a result of the anatomic arrangement of the lymphatics of the skin, as discussed by Keeney. The demonstration at autopsy of involvement of the inguinal and aortic lymph nodes lends support to the work of Furuta that the distant metastases to the skin are a combination of blood borne and lymphatic spread.

SUMMARY

A case of cutaneous metastases from transitional cell carcinoma has been reported. Review of available literature shows this to be the eleventh such case reported.

REFERENCES

COMMITTEE ON CARCINOMA REGISTRY: Cancer of the bladder. A study based on 992 epithelial tumors of the bladder in the carcinoma Registry of the American Urological Association. J. Urol., 31: 423–472, 1934.

FURUTA, S.: Spread of cancer metastases in skin. Arch. f. Dermat. u. Syph., 147: 251–258, 1924.

HIGGINS, C. C. AND HAUSFELD, K. F.: Cutaneous metastases from carcinoma of the urinary bladder: report of 2 cases. J. Urol., 59: 879–886, 1948.

KEENEY, E. L.: Primary carcinoma of trachea with cutaneous carcinomatosis. Bull. Johns Hopkins Hosp., 61: 411–420, 1937.

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REPAIR OF EXSTROPHY OF THE BLADDER

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Repair of exstrophy of the bladder is pretty well confined to implantation of the ureters into the bowel and repair of the abdominal defect, after excision of the exstrophied bladder, by overfolding the anterior fascia-sheaths of the rectus

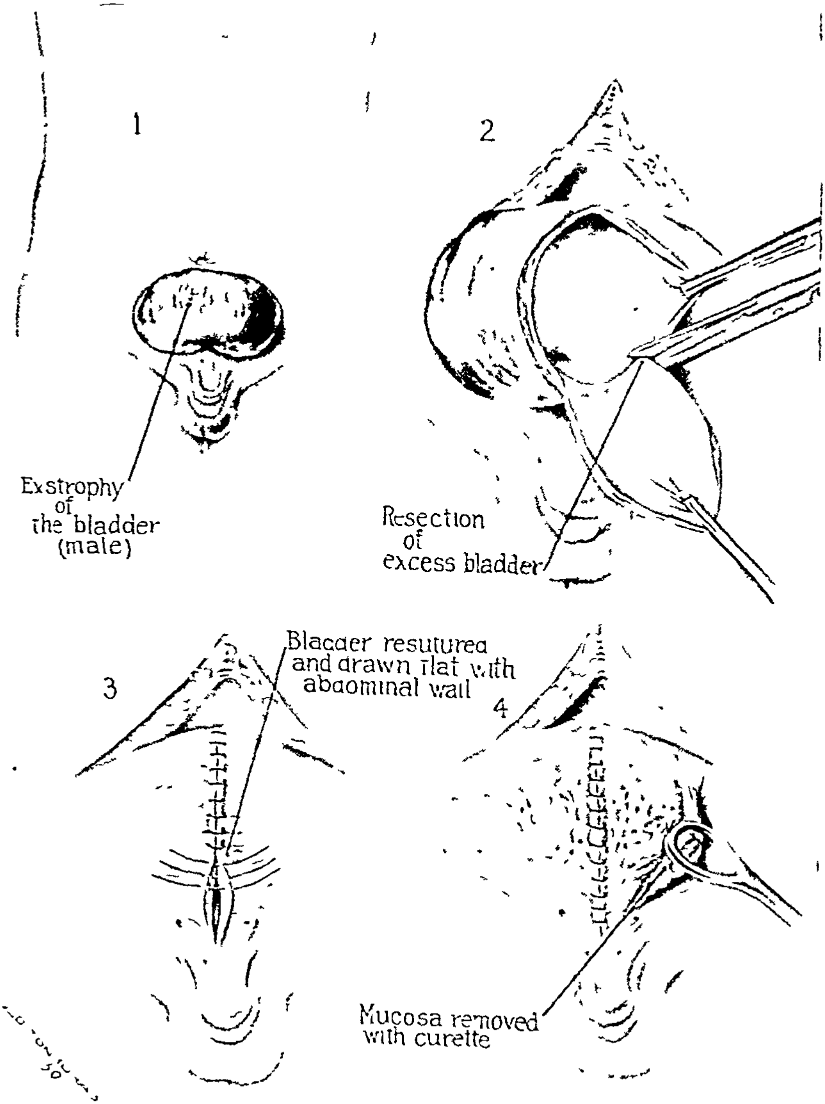
1
Exstrophy of the bladder (male)
2
Resection of excess bladder
3
Bladder resutured and drawn flat with abdominal wall
4
Mucosa removed with curette

FIG 1

muscles. The purpose of this communication is to suggest an improvement in the repair of the abdominal defect.

In my early operations on removal of the exstrophy of the bladder, I was much impressed with the thickness of the bladder muscle and felt that this structure should be utilized in the closure of the abdominal defect rather than being entirely wasted by resection.

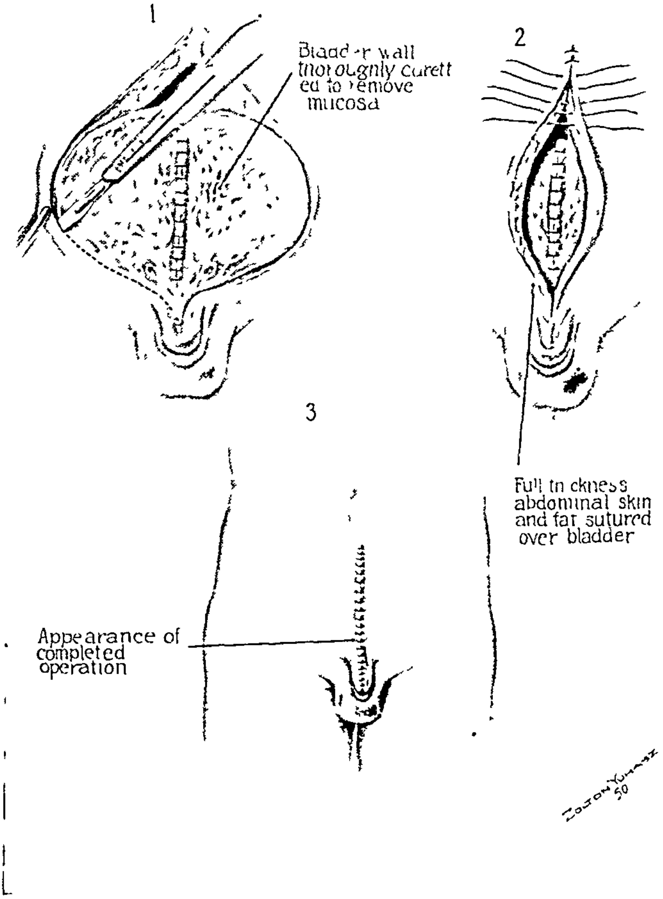
1
Bladder wall thoroughly curett ed to remove mucosa
2
Full thickness abdominal skin and fat sutured over bladder
3
Appearance of completed operation

Fig. 2

In my recent cases, I have utilized this bladder structure by trimming it down to correct size, resuturing it, and curetting off the mucous membrane. The rectus muscle sheaths are left intact, the skin is undermined and brought over on top of the recut and curetted bladder muscle where I have found it grows well and the resulting closure is a very satisfactory, solid, abdominal wall.

Figures 1 and 2 illustrate the procedure. I very strongly recommend it as both simple and efficient.

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EXSTROPHY OF THE BLADDER COMPLICATED BY ADENOCARCINOMA

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As far as we have been able to determine, only 29 cases of carcinoma in an exstrophied bladder have been reported in the literature. In 24 of these cases, the malignant lesion was an adenocarcinoma; in 2 cases, it was a squamous cell epithelioma. In the 3 remaining cases, the type of carcinoma was not stated.

In the years 1909 to 1944, inclusive, 170 cases of exstrophy of the bladder were observed at the Mayo Clinic. Adenocarcinoma was present in the exstrophied bladder in 7, or 4 per cent, of these cases. We shall report 4 of the 7 cases in this paper. Of the 3 remaining cases, 2 have been reported previously by Scholl and 1 has been reported by Judd and Thompson. In addition Scholl mentioned a third case but did not report it in detail. Therefore, we are reporting this case.

REPORT OF CASES

Case 1.—A single woman, aged 38 years, came to the clinic in December 1925, because of a congenital deformity of the bladder and pain in the region of the right kidney. When she had been a child, she had had attacks of pain on the right side. These attacks had been associated with suppression of urine on the right side. Prior to November 1925, she had not had any pain in this region for 15 years. On this date, she had had an attack of severe renal pain which had been followed by fever and general malaise.

Examination of the thyroid gland disclosed a small nodule that was tender to pressure. The patient had a left inguinal hernia and complete exstrophy of the bladder. The mucous membrane of the exstrophied bladder was covered by a large, fungating mass which was dark red in color and bled easily. The orifices of the ureters were not visible. The blood pressure was 140 mm. of mercury systolic and 100 mm. diastolic. The erythrocytes and leukocytes numbered 4,280,000 and 10,400 per cubic millimeter of blood respectively, and the value for the hemoglobin was 61 per cent. The Wassermann reaction on the serum was negative. Roentgenologic examination disclosed an enlarged right kidney and congenital absence of both pubic bones. After indigo carmine had been injected intravenously, it appeared on the left side of the vesical mass but there was no evi-

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Abridgment of thesis submitted by Dr. Goyanna to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology.

[1] One of these cases also was reported by Judd and Thompson.

dence of excretion of the dye from the right ureter. The orifice of the right ureter was located and a Garceau catheter was inserted. As soon as the tip of the catheter had been passed through the vesical portion of the ureter, urine flowed freely and 600 cc were collected. Microscopic examination of this specimen disclosed pyuria, grade 4 (on the basis of 1 to 4) and erythrocyturia, grade 3. Microscopic examination of a specimen of the vesical mass disclosed adenocarcinoma. The diagnosis was adenocarcinoma of the exstrophied bladder and an infected hydronephrotic kidney on the right side.

The hydronephrotic kidney was removed on December 28, 1925. The left ureter was transplanted into the sigmoid colon on January 20, 1926. On February 8, the vesical mucosa, including the malignant lesion, was removed by cauterization. The convalescence was satisfactory. When the patient was seen at the clinic 5 months later, she had gained 5 pounds (2.3 kg.) and she was able to retain the urine in her rectum for from three to five hours. At that time, the value for the urea was 30 mg. per 100 cc of blood.

On June 15, 1926, the patient was brought to the clinic because of severe cramplike pain in the region of the left kidney. The pain was associated with vomiting and a high temperature. As far as could be determined, she had not passed any urine for about 10 hours. Examination revealed a very tender mass in the left upper quadrant of the abdomen. The value for the urea was 178 mg. per 100 cc of blood. Nephrostomy was performed as an emergency procedure.

On January 26, 1932, a stone was removed from one of the calyces of the remaining kidney. At that time, the value for the urea was 22 mg. per 100 cc of blood and the blood pressure was 194 mm. of mercury systolic and 54 mm. diastolic. Between this date and 1935, four renal stones were passed through the nephrostomy tube. When the patient returned to the clinic for examination in 1938, her blood pressure was 254 mm. systolic and 165 mm. diastolic, and the value for the urea was 48 mg. per 100 cc of blood.

On December 4, 1940, the patient was brought to a hospital because of oliguria and because the nephrostomy tube was not draining properly. The values for the urea and creatinine were 244 mg. and 11.2 mg. per 100 cc of blood respectively. The value for the chlorides was 683 mg. per 100 cc of plasma and the carbon dioxide combining power of the plasma was 24.9 volumes per 100 cc. Medical treatment produced only slight improvement in the patient's condition and she died of pulmonary edema on December 12. Necropsy disclosed nephrolithiasis and pyelonephritis. The opening of the ureter in the sigmoid colon was patent but small. There was no evidence of recurrence or metastasis of the vesical neoplasm.

Case 2.—A woman, aged 65 years, who had complete exstrophy of the bladder came to the clinic on September 24, 1931. In 1929, biopsy had disclosed carcinoma of the exstrophied bladder and the malignant lesion had been fulgurated. Shortly before the patient came to the clinic, she had noticed an increase in the amount of vesical mucosa. The only other symptom was dyspnea on exertion, which had been present for 12 or 15 years.

Examination revealed slight enlargement of the heart. The blood pressure was

140 mm. of mercury systolic and 80 mm. diastolic. The value for the urea was 33 mg. per 100 cc of blood. Urinalysis disclosed erythrocyturia, grade 2, and an occasional leukocyte. A considerable amount of redundant mucosa was observed at two points. Biopsy disclosed inflammation of glandular mucous membrane. The redundant mucosa was shaved off and the denuded portions were treated by deep electrocoagulation.

In 1937, the patient returned to the clinic because she again had noticed an increase in the amount of vesical mucosa. Excretory urography disclosed ptosis of the right kidney, calyectasis, grade 2, on the left side, and dilatation of both ureters. Roentgenologic examination also disclosed congenital absence of the symphysis pubis. Examination of the mucosa of the exstrophied bladder revealed three rounded, granular cyanotic masses. Biopsy disclosed adenocarcinoma, grade 1. The involved portions of the mucosa were treated by deep electrocoagulation.

When the patient returned to the clinic for examination 9 months later, the mucosa of the bladder appeared normal but palpation disclosed infiltration at three places. Biopsy again revealed adenocarcinoma, grade 1. The lesions were treated by deep electrocoagulation.

On May 6, 1944, the patient returned to the clinic because she had noticed a mass, about 3 cm. in diameter, on the vesical mucosa. The tumor was obstructing the orifice of the left ureter. Biopsy again revealed adenocarcinoma, grade 1, and the lesion was treated by deep fulguration. The results of excretory urography were the same as they had been in 1937. Fulguration was repeated on June 22, 1945. At that time, the patient's general health was good and she still was very active although she was 80 years of age.

Case 3.—A woman, aged 21 years, came to the clinic on September 17, 1934, because of exstrophy of the bladder and prolapse of the uterus. The prolapse of the uterus first had occurred 4 months before the patient came to the clinic. In 2 or 3 days, the uterus had returned spontaneously to the vagina but the prolapse had recurred 1 month before the patient came to the clinic.

The erythrocytes and leukocytes numbered 4,450,000 and 9,600 per cubic millimeter of blood respectively, and the value for the hemoglobin was 15.4 gm. per 100 cc of blood. A flocculation test for syphilis was negative. The value for the urea was 22 mg. per 100 cc of blood. The blood pressure was 140 mm. of mercury systolic and 80 mm. diastolic. Roentgenographic examination revealed a wide separation of the pubic bones and a deformity of the coccyx. Excretory urography disclosed slight dilatation of the pelvis and calyces of the right kidney and dilatation of the lower half of each ureter. Urine was collected by catheterizing each ureter. Examination of each specimen revealed albuminuria, grade 1, and erythrocyturia, grade 1. Examination of the urine obtained from the left ureter revealed an occasional leukocyte. The mucosa of the exstrophied bladder appeared normal on inspection.

On September 27, 1934, the right ureter was implanted into the sigmoid. The left ureter was implanted similarly on November 22. On December 17, the exstrophied bladder was removed extraperitoneally and the prolapsed uterus was returned to the vagina. Microscopic examination of the bladder disclosed adenocarcinoma, grade 1. About 12 days after the bladder had been removed, the erythrocyte count was 3,680,000 and the leukocyte count was 9,700 per cubic millimeter of blood respectively. The value for the hemoglobin was 11.1 gm. per 100 cc of blood and the value for the blood urea was 38 mg. per 100 cc.

On July 2, 1935, the patient consulted her family physician because of slight stiffness of the neck, muscular weakness and inability to stand on her feet. These symptoms disappeared in 2 days. The muscles and tendon reflexes appeared to be normal. Glycine was administered. The patient had a similar attack in August 1935. She was unable to move her legs and was forced to remain in bed for some time. Her neck was slightly stiff and her arms were weak. Her legs were entirely flaccid and the patellar reflexes were absent. Subsequently, she had several attacks of a similar nature. The attacks usually occurred just before or in the course of a menstrual period.

On October 27, the patient became very drowsy and complained of headache and nausea. Coma developed gradually and the patient died without regaining consciousness. Necropsy revealed that death was due to chronic glomerular nephritis and uremia. There was no evidence of recurrence or metastasis of the adenocarcinoma.

Case 4.—A man, aged 49 years, came to the clinic on May 22, 1944, because of complete exstrophy of the bladder and epispadias. The mucosa of the exstrophied bladder bled easily when it was touched or rubbed. Leukoplakia was present on a considerable portion of the vesical mucosa and the presence of carcinoma was suspected.

The blood pressure was 148 mm. of mercury systolic and 90 mm. diastolic. The erythrocyte and leukocyte counts were 3,850,000 and 21,000 per cubic millimeter of blood respectively, and the value for the hemoglobin was 15.0 gm. per 100 cc of blood. The value for the blood urea was 32 mg. per 100 cc, the concentration of chlorides was 621 mg. per 100 cc of plasma, and the carbon dioxide combining power of the plasma was 42.8 volumes per 100 cc. The sedimentation rate of the erythrocytes was 32 mm. in 1 hour. Roentgenographic examination revealed extensive separation of the pubic bones. Excretory urography disclosed the following findings: dilatation, grade 2, of the pelvis of the right kidney; dilatation, grade 1 to 2, of the calyces of the right kidney; dilatation, grade 2, of the upper third of the right ureter and dilatation, grade 3, of the lower third of this ureter; evidence of reduced function of the left kidney; suggestive evidence of dilatation of the calyces of the left kidney, and dilatation, grade 1, of the left ureter throughout its entire extent.

Bilateral ureterosigmoidostomy was performed on June 1. On July 7, the exstrophied bladder was removed and the epispadias was repaired. Microscopic examination of the bladder revealed adenocarcinoma, grade 1.

The patient's convalescence was complicated by acute parotitis and bronchopneumonia. He was dismissed from the hospital on July 24, 1944.

PATHOLOGY

It has long been known that glands are present in the mucosa of an exstrophied bladder. The close relationship between the embryology of the bladder and that of the rectum has suggested several explanations for the histogenesis of these glands and the development of carcinoma in an exstrophied bladder. Ehrich suggested several hypotheses to explain the presence of these glands. The

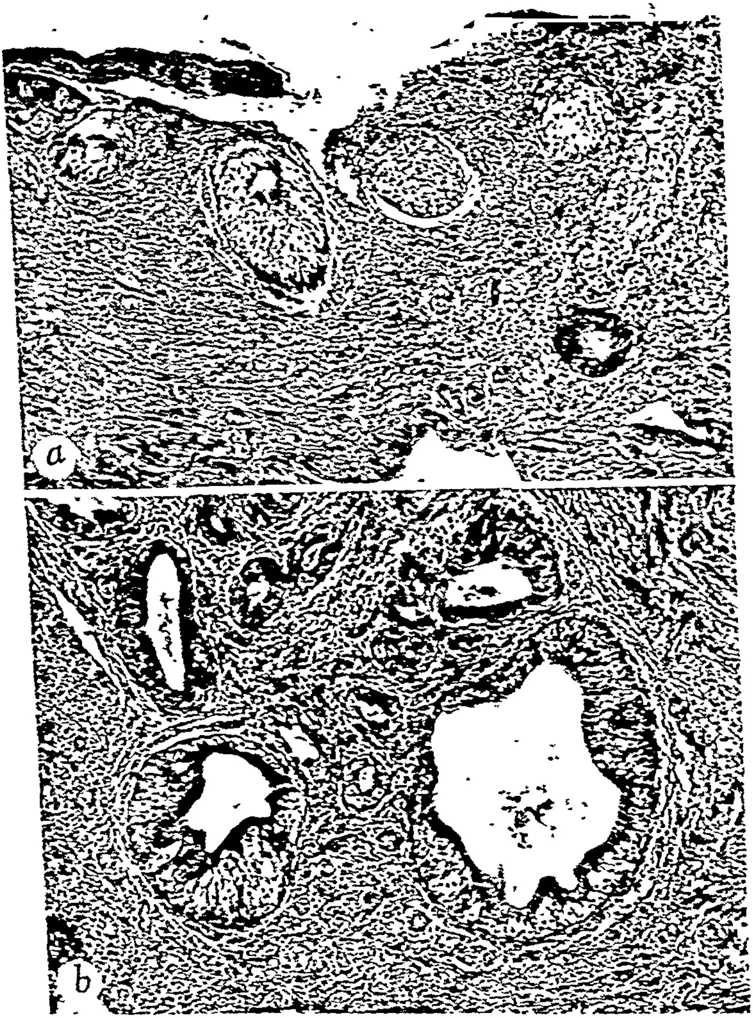

FIG. 1. *a*. Section of exstrophied bladder showing formation of glands from epithelial cell nests. Two nests are visible at right. In middle of left side is 1 larger nest in which a lumen is beginning to form (hematoxylin and eosin stain; × 90). *b*. Section showing more advanced stages of formation of glands. On left, lumen is enlarged and marginal cells have begun to assume a cylindric appearance. On right, cells are typically columnar and there is some secretion of mucus (hematoxylin and eosin stain; × 90).

one that he favored most was that a displaced or underdeveloped spur of cloacal entoderm (Rathke's spur) caused inclusion of embryonic epithelium of the rectal type in the vesical wall. This view was supported by 9 cases of exstrophy of the bladder which had been reported previously by Hache. In these cases, some portion of the intestine opened directly onto the surface of the exstrophied bladder. Lacène and Hovelacque, Dupont and Gayet believed that these glands represented a true ectopy of undifferentiated cells from the primitive intestine. Reichel expressed the opinion that the cloacal epithelium failed to differentiate into vesical epithelium; as a result, the bladder contained glands like those in the rectum. Remedi expressed the opinion that glands, either of vesical or rectal origin, become abnormal at an early period and persist throughout life. Judd and Thompson said that it is logical to assume that the presence of glandular tissue in the bladder is due to cell inclusion.

Enderlen found only transitional epithelium in the exstrophied bladders of a number of infants who died at birth. Formiggini failed to find any cylindrical cells or glands in the exstrophied bladder of an infant who was 9 days old. According to Aschoff, the exstrophied bladder of a newborn infant is covered by normal vesical mucosa; in adult life, mucous glands develop and the mucosa resembles that of the rectum.

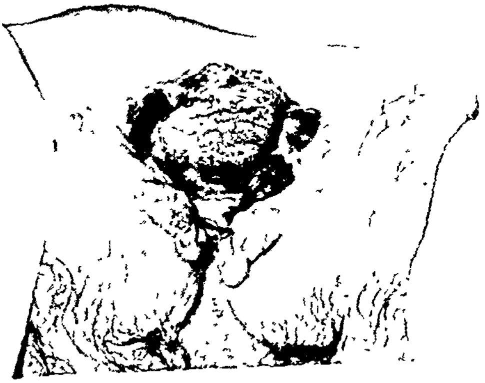

FIG. 2. Gross appearance of adenocarcinoma of exstrophied bladder of a female patient (case 2).

It is possible that the presence of glandular mucosa in an exstrophied bladder is caused by metaplasia. In one of the cases reported in this paper (case 3), we were able to observe the formation of glands from epithelial invaginations of the Limbech-Brunn type (fig. 1, *a* and *b*).

The low grade of malignancy of adenocarcinoma of an exstrophied bladder and the histologic appearance suggest that the neoplasm develops in benign glandular mucosa. Although it is possible that adenocarcinoma may originate in remnants of the urachus, there was no evidence that the neoplasm originated in this manner in any of the 7 cases which form the basis of our report.

Gross appearance.—The involved portion of the mucosa usually was redundant.

dark red in color, and bled easily (fig. 2). A considerable amount of leukoplakia was present in 1 case. There was no evidence of invasion of the adjacent skin in any case.

Microscopic appearance.—The microscopic appearance of the tumor was identical in each case. The tumors contained intestinal glands which were composed of tall columnar cells that secreted mucus (fig. 3). The glands frequently had a papillary appearance. There was no evidence of infiltration of the deeper layers. Transitional and squamous epithelium was seen in all cases. Cornification of the squamous epithelium was observed frequently. In all of the seven cases, the malignancy of the adenocarcinoma was grade 1, as determined by the method of Broders.

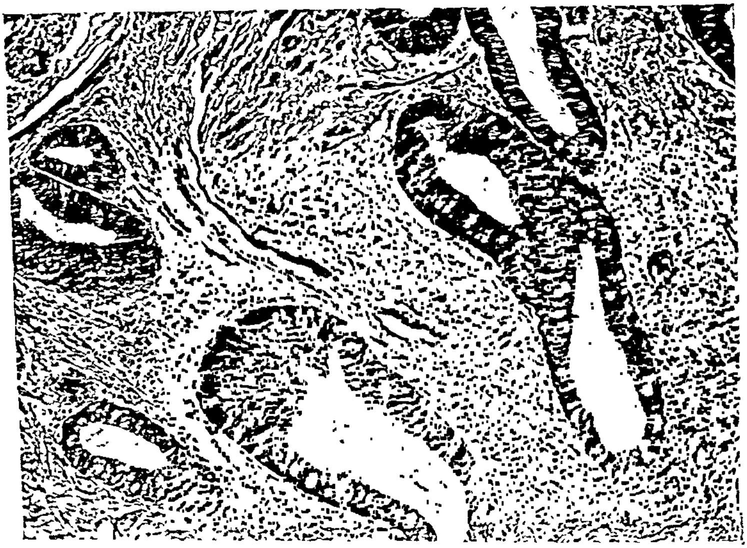

FIG. 3. Adenocarcinoma, grade 1, of exstrophied bladder. Mucus can be seen in goblet type cells and also extracellularly (Dresbach's mucus stain; × 90).

SYMPTOMS AND SIGNS

In 5 of the 7 cases in this series, the patients had noticed a steadily growing mass on the vesical mucosa. Most of the patients observed an increase in the burning sensation and aching in the exposed mucosa. In some cases, an increase in the amount of bleeding from the mucosa causes the patients to consult a physician. In one case, gross examination did not reveal any evidence of disease of the bladder.

TREATMENT

In contrast with adenocarcinoma of the normally situated bladder, adenocarcinoma of the exstrophied bladder is of a low grade of malignancy and rarely causes death. In our opinion, the treatment of choice is bilateral implantation of the ureters and total cystectomy. If this treatment is contraindicated, local ex-

TABLE 1. *Results of treatment of adenocarcinoma occurring in an exstrophied bladder*

CASE	SEX	AGE	TREATMENT	RESULTS	POSTMORTEM FINDINGS
		yrs.			
1	F	38	Removal of right kidney; left ureter implanted into sigmoid; bladder removed by cauterization; subsequent nephrostomy and removal of stone from left kidney	Patient died of pyelonephritis, 15 yrs. after diagnosis of malignant lesion	Nephrolithiasis and pyelonephritis; no evidence of recurrence or metastasis of malignant lesion
2	F	65	Electrocoagulation of tumor; recurrent lesions treated by electrocoagulation and fulguration	Patient living 16 yrs. after diagnosis of malignant lesion	
3	F	21	Bilateral ureterosigmoidostomy and cystectomy	Patient died of chronic glomerular nephritis and uremia, ten months after diagnosis of malignant lesion	Chronic glomerular nephritis; no evidence of metastasis or recurrence of malignant lesion
4	M	49	Bilateral ureterosigmoidostomy and cystectomy	Patient living, six months after diagnosis of malignant lesion	
5*	F	23	Bilateral ureterosigmoidostomy and cystectomy	Patient died of recurrence and possible metastasis of malignant lesion, two years after diagnosis	Necropsy not performed
6†	M	48	Local excision of tumor and radiotherapy	Patient died of cerebral hemorrhage, 7 yrs. after diagnosis of malignant lesion	No evidence of metastasis or recurrence of malignant lesion
7†	F	38	Bladder excised by cauterization	Patient living and in good health, 19 yrs. after diagnosis of malignant lesion	

* Reported previously by Scholl.

† Reported previously by Judd and Thompson.

cision or simple fulguration may prove satisfactory if the patient can be emaxined periodically after the operation.

The treatment employed in this series of 7 cases and the results of the treatment are shown in table 1.

As adenocarcinoma occurs in about 4 per cent of exstrophied bladders, the ureters should be implanted into the rectum and cystectomy should be performed in order to prevent the development of this tumor.

SUMMARY

In the years 1909 to 1944 inclusive, 170 cases of exstrophy of the bladder were observed at the Mayo Clinic. Adenocarcinoma of the exstrophied bladder was present in 7, or 4 per cent, of these cases. This report is based on 4 of these 7 cases. Adenocarcinoma of the exstrophied bladder is of a low grade of malignancy and rarely causes death. The treatment of choice is bilateral implantation of the ureters and total cystectomy. Local excision or simple fulguration may be satisfactory if the patients can be examined periodically after the operation. Implantation of the ureters and total cystectomy should be performed in order to prevent the development of adenocarcinoma in cases of exstrophy of the bladder.

REFERENCES

Abeshouse, B. S.: Exstrophy of the bladder complicated by adenocarcinoma of the bladder and renal calculi; a report of a case and a review of the literature. J. Urol., **49:** 259–289, 1943.

Aschoff, Ludwig: Pathologische Anatomie; ein Lehrbuch für Studierende und Ärtze. Jena: C. Fischer, 1928, vol. 2, pp. 502–503.

Bergenhem: Quoted by Lecène, P. and Hovelacque, A.

Dupont, Robert: A propos d'un cas de cancer développé sur une vessie exstrophiée. J. d'urol., **13:** 433–444, 1922.

Ehrich, E.: Gallertkrebs der ekstrophierten Harnblase. Gleichzeitig ein Beitrag sum Maydl'schen Operationsverfahren der Blasenektopie. Beitr. z. klin. Chir., **30:** 581–604, 1901.

von Eiselsberg: Fall von Karzinom der Schleimhaut einer Blasenektopie vor, der vor fünfviertel Jahren operiert wurde. (abstr.) Wien. klin. Wchnschr., **19:** 548–549, 1906.

Enderlen: Zur Histologie der Schleimhaut der ektopierten Blase. Verhandl. d. deutsch. path. Gesellsch., **7:** 167–170, 1904.

Enderlen: Quoted by Lecène, P. and Hovelacque, A.

Formiggini, Benedetto: Contributo allo studio istologico della mucosa vescicale extrofica. Riforma med., **36:** 252–254. 1920.

Gayet, Robert: Un cas d'exstrophie vésicale cancérisée. J. d'urol., **39:** 295–307, 1935.

Geraghty, J. T.: Tumors of the Bladder. In Cabot, Hugh: Modern Urology; Diseases of the Bladder—Diseases of the Ureter—Diseases of the Kidney. Philadelphia; Lea & Febiger, 1918, vol. 2, chap. 7, pp. 187–244.

Goyanna, R., McDonald, J. R. and Emmett, J. L.: Adenocarcinoma of the normally placed urinary bladder. Unpublished data.

Graham, W. H.: Ectopia vesicae complicated by adenocarcinoma, with review of literature. Brit. J. Surg., **30:** 23–32. 1942.

Hache, Maurice: Pathogénie et variétés de l'exstrophie de la vessie. Rev. de chir., Paris, **8:** 218–227, 1888.

Hager, August: Ekstrophia vesicae urinariae mit Adenocarcinoma gelatiniforme. Müchen. med. Wchnschr., **2:** 2301–2304, 1910.

Hammer, E.: Cancer du colon sigmoide dix ans après implantation des uretères d'une vessie exstrophiée. J. d'urol., **28:** 260–263, 1929.

Hunner, G. L.: Quoted by Kelly, H. A. and Burnam, C. F.: Diseases of the Kidneys, Ureters and Bladder; With Special Reference to the Diseases in Women. New York; D. Appleton and Company, 1914, vol. 2, p. 389.

Judd, E. S. and Thompson, H. L.: Exstrophy of the bladder complicated by carcinoma. Arch. Surg., **17:** 641–657, 1928.

Lampe: Demonstration eines Präparats von Carcinom der Harnblase bei Ectopia Vesicae. Verhandl. d. deutsch. Gesellsch. f. Chir., **34:** 226, 1905.

Lecène, P. and Hovelacque, A.: Les cancers développés sur la vessie exstrophiée. J. d'urol., **1:** 493–502, 1912.

Lower, W. E.: Exstrophy of the urinary bladder with carcinoma. Ann. Surg., **73:** 354–356, 1921.

McCarthy, J. F. and Klemperer, Paul: Report of interesting case of exstrophic bladder with neoplastic implant. Tr. Am. A. Genito-Urin. Surg., **18:** 67–75, 1925.

McCown, P. E.: Carcinoma in exstrophy of the bladder. J. Urol., **43**: 533–542, 1940.

Montpelier, Goinard, Karsente and Mele: Quoted by Graham, W. H.

Murphy, D. P.: Exstrophy with cancer of bladder and absence of umbilicus; report of case. J. A. M. A., **82**: 784–785, 1924.

Reichel: Quoted by Judd, E. S. and Thompson, H. L.

Remedi: Quoted by Formiggini, Benedetto.

Righetti: Quoted by Formiggini, Benedetto.

Sargent, P.: Case of epithelioma developing in the scar of a plastic operation for extroversion of the bladder. Brit. J. Child. Dis., **6**: 115–116, 1909.

Scheuer, P.: Über einen Fall von Blasenektopie mit carcinomatöser Degeneration der Blasenschleimhaut. Ztschr. f. urol. Chir., **30**: 299–308, 1930.

Schloffer: Karzinom der ektopischen Blase. (abstr.) Wien. klin. Wchnschr., **23**: 1158, 1910.

Scholl, A. J., Jr.: Histology and mortality in cases of tumor of the bladder. Surg., Gynec. & Obst., **34**: 189–198, 1922.

Scholl, A. J.: The potential malignancy in exstrophy of the bladder. Ann. Surg., **75**: 365–371, 1922.

Shattock, S. G.: Specimens of epispadias and extroversio vesicae showing an attachment of the muscular wall of the bladder to the back of the pubic bones, etc. Tr. Path. Soc., London, **45**: 117–124, 1894.

Wagner, A.: Kankroid der ekstrophierten Harnblase. Deutsche Ztschr. f. Chir., **104**: 329–334, 1910.

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MYOSARCOMA OF THE BLADDER

GEORGE M. FISTER AND ANTHONY J. LUND

Any type of sarcoma of the urinary bladder is a rare disease, and the myosarcomas are apparently less frequently encountered than are the other types. Perhaps a more rare occurrence than the appearance of the tumor, is the incidence of having had, during 1948, two patients with sarcoma of the bladder. One was a leimyosarcoma, the other a rhabdomyosarcoma.

It is these two case reports that are the subject of this paper.

CASE REPORTS

Case 1. H. E. C., a white man, aged 62, was admitted to the hospital on January 5, 1948, with the complaint of "bloody urine." The family history was negative except that one brother had died of tuberculous pharyngitis (?).

The patient's past health had always been good except for an appendectomy in 1945, and the removal of a new growth (no pathological report available) from the lower lip in 1946.

The present illness started about 3 months before admission, when the patient noticed that his urine contained blood. Since the onset, the hematuria had occurred at irregular intervals, but during the last 3 weeks the bleeding had been more severe. There had been some dysuria, frequency and nocturia, but no chills, fever, or pain.

On physical examination the patient did not appear ill. The blood pressure was 140/80. The skin was normal, and there were no enlarged lymph glands. The heart and lungs were normal. The abdomen was soft, and there were no palpable masses. On rectal examination, the prostate gland was soft and movable, with a grade one enlargement. On January 7, 1948, under pentothal anesthesia, the patient was examined with the cystoscope, and there was found a necrotic bleeding tumor, involving the right lateral wall of the bladder. The right ureteral orifice was not seen. With a Stern-McCarthy resectoscope, a portion of the tumor was removed for biopsy. The pathological report by Dr. E. D. Zeman on this tissue was as follows:

"*Microscopic:* The tissues are largely necrotic masses of fibrin, fibroblastic elements and extravasated red blood cells. In the tissues not so involved, there are masses of spindle cells with rather prominent cystoplasmic extensions. The nuclei are central, large, and irregular, with numerous mitotic divisions of irregular order. Associated stroma is lacking. In some sections longitudinal striations of the fibres are apparent. No transverse striations are visible. Diagnosis: Sarcoma (leiomyosarcoma) of the urinary bladder." (See figure 1.)

Radiographic report on examination of the chest showed the lungs clear and the heart normal for size and configuration.

Laboratory reports: Urine: albumin 75 mg. per cent; sugar, none; pus, 2 plus; and much blood. Urea nitrogen 18.9 mg. per cent; blood Kahn negative blood count: hemoglobin 14.5 gm., hematocrit 45, white blood count 12,800.

After the foregoing examination and pathological report, we decided that additional therapy should be either total cystectomy with bilateral ureteral transplantation, or if possible, resection of the tumor and the involved right bladder wall.

On January 15, 1948, a cystotomy was performed. Upon entering the bladder, a large grayish red mass, with origin on the right lateral wall of the bladder, was seen about 4 cm. posterior to the right ureteral orifice. A catheter was passed up the right ureter and the tumor bearing area with the bladder wall was resected. The tumor was very friable with a necrotic surface. It was approximately 7 cm. in diameter, while the base or pedicle was only 2 cm. in diameter. Bleeding was controlled by fulguration and ten radon seeds with a total of 20.5 millicuries were implanted in the area adjacent to the base of the tumor. A suprapubic catheter was left in the bladder.

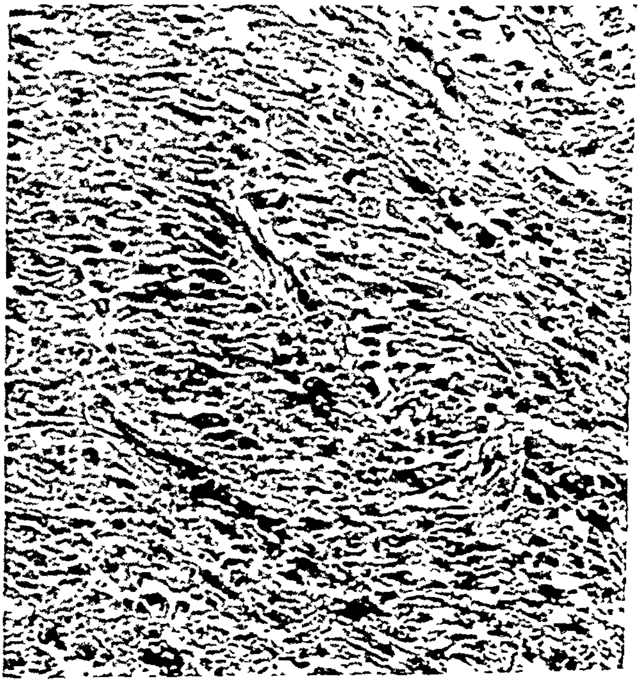

FIG 1. Case 1 Section of tissue removed Diagnosis Leiomyosarcoma of bladder

The postoperative course was uneventful; however, after closure of the suprapubic wound the patient was unable to void. On February 16, 1948, a transurethral resection of the prostate was done and approximately 20 gm. of tissue removed. (Pathological report: Benign hyperplasia of the prostate.) At this time no tumor was seen in the bladder. The patient was discharged on February 24, 1948. The suprapubic wound was closed and urination was free.

On March 5, 1948, ten days after discharge from the hospital, the patient returned because of continued hematuria and pain. At this time the patient appeared anemic. Temperature 101 F. Gross hematuria was present and a tender bluish induration was palpable in the suprapubic area. The diagnosis was probable *extravasation of* urine through the previous cystotomy wound. On March 9, under pentothal anesthesia, a midline incision was made above the pubis. Extravasation of blood and necrotic tissue were found about the bladder and in the space of Retzius. The bladder was opened and many clots and pieces of necrotic grayish-red tissue were removed. The pathological diagnosis on a piece of this tissue was leiomyosarcoma of the urinary bladder.

Following this, the patient's course was rapidly "down hill" with an even more rapid local growth of the tumor. The mass made a mushroom like appearance protruding through the suprapubic wound (fig. 2).

The laboratory reports of interest were: blood alkaline phosphatase 16.5 units; acid phosphatase 3.3 units; the highest nonprotein nitrogen 32.7 mg. per cent; urea nitrogen 15.2 mg. per cent; sedimentation rate 60 mm. 1 hour; blood hemoglobin 10 gm.; hematocrit 26; red blood count 3,250,000; white blood count 41,000. Death occurred on March 28, 1948, six months after the onset of symptoms, or 3 months after the patient entered the hospital.

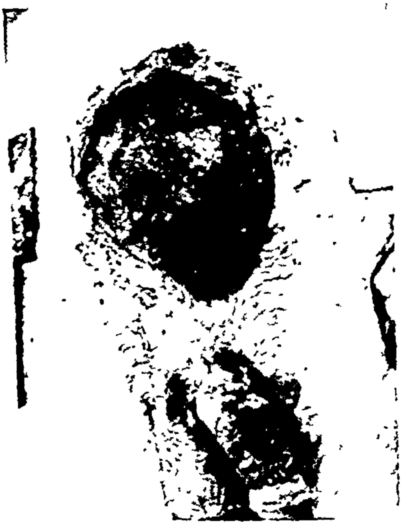

FIG. 2. Case 1. Photograph of tumor shortly before patient's death

Post-mortem examination, March 28 (abstract): An ulcerating necrotic mass was present on the lower abdomen, overriding the symphysis pubis, and upward to about 2 cm. below the umbilicus. The mass was elevated about 6–8 cm. above the abdominal wall and the base was about 15 cm. in diameter. The mass was soft, somewhat necrotic and hemorrhagic in appearance. The urinary bladder was almost entirely filled with this friable, red-gray, fragmented mass. This tumor extended in an explosive type of growth into and above the anterior abdominal wall. In the cortex of each kidney were many small yellow abscesses, ranging from 6 to 8 mm. in diameter.

Microscopic: Tumor mass, the findings were the same as noted in the resected tumor tissue. In some of the tumor tissue there were wide vascular spaces which were choked with tumor cells. This was especially noteworthy since no distinct metastasis was found. Death was probably due to the rapidity of the growth of the tumor, bleeding and bilateral pyelonephritis with cortical abscesses. Diagnosis: Leiomyosarcoma of the urinary bladder, bilateral cortical renal abscesses.

DISCUSSION

Lex and Bell, in a review of the literature in 1947, found 22 recorded cases of leiomyosarcoma of the urinary bladder and made a report of 1 case that they studied. Mackles et al. in 1948 reported a case of carcinoma and leiomyosarcoma of the bladder. A summary showed that all of the 23 patients except 3 had died within a year after the onset of symptoms. This also holds true for our patient, who died about 6 months after the first onset of hematuria.

These tumors do not usually metastasize, but local growth and recurrence are rapid. Of the 24 reported cases, metastasis occurred only in two.

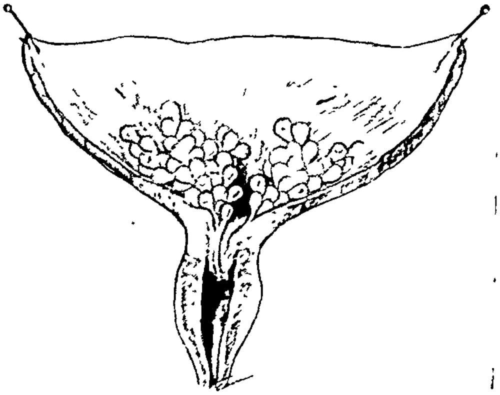

FIG. 3. Case 2. Artist's conception of tumor during early stage of development

Our experience, as viewed by this one case, would suggest the following: 1) One should make the diagnosis of leiomyosarcoma of the bladder by transurethral removal of tissue and biopsy. 2) The bladder should not be opened. 3) Transplantation of the ureters with total cystectomy of the closed bladder would seem the method of choice.

This conclusion seems correct when one considers the rapid recurrence of the tumor in the cystotomy wound of our patient. Undoubtedly sarcoma cells were widely scattered when resection of the tumor and bladder wall was done. Post mortem examination of the patient failed to show metastasis and death was due to local recurrence and kidney infection. If a careful cystectomy had been done, with ureteral transplantation, the result might have been better.

Case 2. R. H. was admitted to the hospital on July 10, 1948 at the age of 10 months with the complaint of straining upon urination and terminal hematuria of several weeks' duration. Physical examination was noncontributory. The urinalysis showed 15–20 red blood cells and 3–5 white blood cells per high power field. Excretory urography showed a soft tissue filling defect involving the base of the bladder. Cystoscopic examination disclosed a polypoid tumor arising from the bladder neck and posterior urethra.

A cystotomy revealed many grape-like, translucent lesions attached to two pedicles originating from the bladder neck and the posterior urethra. The bladder neck musculature seemed thickened, edematous, and was covered by a shiny epithelium (fig. 3). The grape-like clusters were removed, the base of each pedicle fulgurated, and a section of the bladder neck removed for biopsy.

Microscopic examination of the sections (H. & E. stain) was reported by Dr. R. C. Ellis as follows: "The sections reveal fragments of polypoid mass of loose connective tissue, partly covered by transitional and squamous epithelium. There are some foci of ulceration and necrosis on the surface. In some fields, the surface epithelium dips down to form crypts or pockets beneath the surface. The underlying connective tissue stroma exhibits marked edema and intense inflammatory reaction. Hyperplastic capillaries are numerous. Diagnosis: Polyp of the bladder."

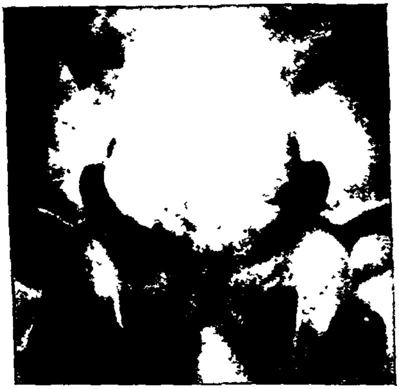

FIG 4. Case 2 Cystogram showing filling defect due to recurrence of tumor (6 months after resection).

The postoperative course was uneventful, and the patient was discharged improved.

The next admission was in September 1948, because of the recurrence of straining and pain upon urination, with intermittent hematuria. Examination showed a healed, midline, suprapubic incision from the previous cystotomy. Cystoscopic examination revealed many "polyps" originating from the bladder neck, trigone, and posterior urethra. Another cystotomy was performed, with excision and fulguration of the polypoid structures. The tissue fragments were again interpreted as multiple polyps. The patient's wound again healed well, he became symptom free, and gained weight.

The patient was again examined in early December. A cystogram showed an irregular filling defect of the base of the bladder (fig. 4). Shortly thereafter, symptoms of bladder neck obstruction again developed, and he was admitted to the hospital. The physical examination was essentially unchanged. A cystoscopy showed similar lesions as described previously. In addition, patches of infiltration of the bladder wall were noted, covered by a red, smooth epithelium. A cystotomy was performed and tissue removed for a section. Phosphotungstic acid hematoxylin was used to stain the tissues, and this time, many elongated cellular fibers with numerous cross straitions were noted. Diagnosis: Rhabdomyosarcoma of the bladder (fig. 5).

The tumor mass grew rapidly, and began to protrude through the abdominal wall. It appeared reddish-yellow, was of firm consistency, was arranged in convolutions and was covered by a smooth and glistening epithelium.

The ureters were then transplanted into the sigmoid colon. The abdominal portion of the mass was excised, removing 1–2 cm. of skin and muscle beyond the site of the tumor. A resection of the prostate, bladder, and membranous urethra was then performed. Grossly, the lesion showed no evidence of infiltration into the abdominal wall, perivesical tissue, or the prostate. Neither the pelvic nor peri-aortic lymph nodes appeared involved.

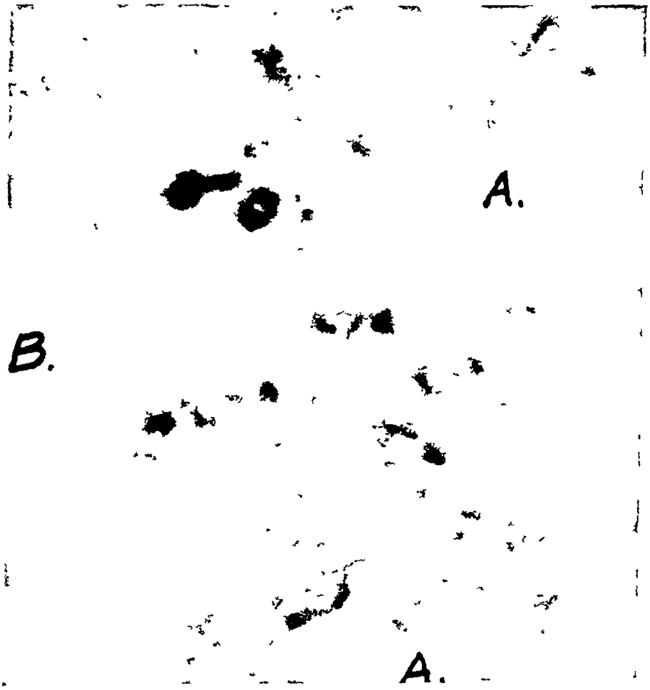

FIG 5 Case 2 Section of tissue removed Diagnosis: Rhabdomyosarcoma of bladder (phosphotungstic acid hematoxylin stain).

The child survived this radical procedure, and the wound healed satisfactorily. He gained weight, and the ureteral transplant functioned satisfactorily. After about six months, a large mass became palpable in the lower abdomen. Partial obstruction of the lower bowel developed, with ensuing emaciation and dehydration. Death occurred on January 3, 1950.

Autopsy showed the presence of a vascular, polypoid, firm tumor involving most of the lower abdomen with compression and infiltration of the rectum and adjacent tissues. Two small metastatic lesions were noted in the lungs. Regional lymph nodes were not involved.

Histologically, the tumor presented essentially the same picture as previously, except for greater cellularity and numbers of mitotic figures.

DISCUSSION

In 1947, Kretschmer reviewed the literature, and including his own report, found 17 cases of rhabdomyosarcoma of the bladder. Meisel, Heath, and Miller reported another instance in March 1949.

On examination of the collected cases, it is worthy of note that 10 were in children under the age of 2½ years, and that in about half the cases the neoplasms were located within or near the trigone and bladder neck. This leads to the speculation that these tumors arise from anomalies of the wolffian duct or embryonal heteratopias. It is to be remembered, however, that striated muscle is present in the sphincter of Henle and has been found in normal prostates; therefore, the lesion could conceivably arise from these elements. (Khoury and Speer). Hirsch and Gasser have suggested that perhaps this tumor is primary in the prostate or retroprostatic tissue rather than the bladder.

Diagnostically speaking, a urologist or pathologist should consider a rhabdomyosarcoma of the bladder in any rapidly growing tumor which presents a polypoid appearance. He should also promptly request that the excised tissue be stained to show evidence of voluntary muscle.

In the case presented, a malignancy was suspected, but could not be proved histologically because ordinary staining methods revealed benign appearing tissue, and with consequent loss of valuable time.

Rhabdomyosarcoma of the bladder has a bad prognosis, the average survival period being 6½ months. Kretschmer reported survival and no evidence of recurrence in his case 4½ years after operation, the tumor being removed by partial cystectomy. This is the only recorded case which has lived a significant period after treatment.

It seems reasonable, however, that since this type of sarcoma apparently metastasizes late, and spreads mainly by direct extension, better results should be obtained by radical resection, if the diagnosis is made early.

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REFERENCES

Hirsch, E. F. and Gasser, G. W.: J. Urol., **51**: 517, 1944.
Khoury, E. N. and Speer, F. D.: J. Urol., **51**: 505, 1944.
Kretschmer, H. L.: Arch. Path., **44**: 350, 1947.
Laughlin, V. C., Althoff, C. C. and Brown, H. W.: J. Urol., **60**: 459, 1948.
Lex, M. and Bell, W. C.: J. Urol., **57**: 251, 1947.
Mackles, A., Immergut, S., Grayzel, D. M. and Cottler, Z. R.: J. Urol., **59**: 1121, 1948.
Meisel H. J. Heath, W. H. and Miller, J. M.: J. Urol., **61**: 525, 1949.

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FUNCTIONAL RESULTS FOLLOWING TRANSURETHRAL RESECTION AND RETROPUBIC PROSTATECTOMY

H. C. ROLNICK AND M. A. ROBBINS

This report is based on a series of patients followed carefully over periods of from 3 to 14 months.

We are particularly concerned with our functional end results following transurethral electroresection for removal of obstruction at the bladder neck due to lesser degrees of hypertrophy, bars and contractures. We should also like to report our results in retropubic prostatectomy.

The mortality from prostatic surgery has reached an almost irreducible minimum. (David Davis.) Improvements in the management of these patients have made prostatic surgery a very satisfactory procedure. Chemotherapy, employment of supportive measures, particularly the administration of blood, improved surgical technique, and improvement in anesthesia have reduced considerably the mortality and morbidity in prostatic surgery. Infection is no longer a serious problem, and hemorrhage, while it is still the one important problem in prostatic surgery with all the operative procedures, is much better controlled at present. The Foley and other bag catheters and the resectoscope have made this possible together with the free administration of blood. Davis has emphasized the value of the resectoscope for the control of early or late postoperative bleeding following any type of open prostatic surgery. We have recently had an experience in the control of bleeding following perineal prostatectomy which brought out the value of the resectoscope. The catheter had to be removed and another catheter could not be inserted because of the distortion of the prostatic bed. This had been our experience in the past, and we can recall 3 instances of severe postoperative bleeding after perineal prostatectomy which could be controlled only by cystotomy and packing of the prostatic bed. It was possible to pass a resectoscope very easily, and thus control the bleeding with the loop electrode and later insert a catheter into the urethra through the lumen of the resectoscope. We have also been able to control bleeding following suprapubic and retropubic prostatectomy with the resectoscope.

In qualified hands the mortality from prostatic surgery, whatever the operative approach, is not more than from 2 to 4 per cent. Only one of our patients died during the past year; he was an 81 year old man who began to bleed immediately postoperative following transurethral resection. This was apparently induced by ephedrine injected by the anesthetist at the end of the operation, for there was an immediate increase of blood pressure from 120 systolic to 200. After considerable effort, the bleeding could be controlled only by suprapubic cystotomy and pack. The patient developed oliguria and died 10 days later. He had recovered from his oliguria, and necropsy showed right heart failure and edema of the lungs which was apparently induced by excessive administration of fluids following his recovery from the acute phase of lower nephron nephrosis.

Read before meeting of the Chicago Urological Society, January 27, 1950.

Thus, instead of either expecting a death in a particular patient or a relatively high mortality rate in a series of cases, the situation is now completely changed so that an operative death should occur very infrequently and that when a death occurs one must try to carefully analyze the cause; for most, except those due to cardiovascular accidents, are avoidable. The question of mortality following prostatic surgery whether open or closed does not present a serious problem any more. Neither is morbidity a very great problem at the present time, for the majority of patients get well quickly, and their hospital stay is, in the main, quite short following any of the four operations. Although the patient is usually discharged from the hospital more quickly following transurethral resection, the period for his recovery is as great, if not greater in many cases, than following the open operations. As a rule he is not able to return to work any sooner. The patient who has had a transurethral resection requires postoperative attention for a longer period of time than does the patient with the open operation. Many months often elapse before the frequency and pain on urination subside.

Secondary hemorrhage, both early and late, may occur after any of these operative procedures. It may be serious, but can be readily controlled in nearly all cases.

We are therefore not so seriously concerned now, as in the past, as to whether we have a live patient, for we can reasonably expect that; nor whether there will be prolonged hospitalization following any of the operative procedures; for the postoperative course is much better controlled now and healing expedited. Thus both the problems of mortality and morbidity have been largely overcome. We are still concerned however with the functional end results. None of the operations for the relief of prostatism are perfect; they all have their shortcomings. It is possible that some form of nonoperative therapy will be developed that will satisfactorily relieve most of the patients suffering with prostatism. However, at the present time surgery is necessary for the relief of prostatic and other bladder neck obstructions. The urologist with experience can get along satisfactorily in most cases with routine use of only one of the operations, whether suprapubic, perineal, retropubic or transurethral. He should however be able to do all, for each of these operations has an occasional superindication. For instance: 1) The stout man with a large prostate and a large abdomen is best operated upon perineally. 2) A large prostate that is bleeding is best removed through the suprapubic route. 3) The small contractures are best handled transurethrally. Furthermore, irrespective of which operation the urologist chooses to do, in most cases, or even routinely, acquaintance with all the routes of approach gives one a better conception of the pathologic anatomy of the prostatic urethra and the bladder neck in the presence of obstruction. One can learn something from each type of operation, for each has its good points which can be applied to any of the others. Thus, in suprapubic prostatectomy, taking a wedge out of the bladder neck and cutting the interureteric ridge, as is done frequently in transurethral resections for bladder neck contracture, and also in retropubic prostatectomy, will help avoid some poor functional results. It is occasionally best to expose the prostate perineally for possible carcinoma and in many cases a more complete cystectomy is done with a combined perineal and suprapubic approach.

This discussion is based upon a review of a series of private patients carefully observed over periods ranging from 3 to 14 months postoperatively. No operations done within the past 3 months are included in this series. This series consists of 150 transurethral resections, and 24 cases of retropubic prostatectomy. Fifteen suprapubic prostatectomies were done and 6 perineal prostatectomies during this period, which we felt were not enough to carefully analyze.

We have had a large experience with transurethral prostatectomy during a period of almost a score of years. The last 150 cases of transurethral resection were chosen because only in recent years have we felt that we had developed a fair degree of facility and experience with transurethral resection. Our experience with retropubic prostatectomy is based on a series of almost 200 cases. The latter operation has been improved upon since Millin first reported his series, and we believe we have added a few points to the technique which has helped simplify it.

TRANSURETHRAL RESECTION

In this series of 150 cases it was possible to follow 131 over a period of 3 to 14 months. These included only benign bladder neck obstruction. In analyzing these 131 cases they were further broken down into the size of the gland. Of 79 resections yielding 20 or less grams of tissue, 59 (72 per cent) were definitely improved. Twelve others continued to have symptoms over periods lasting from 3 to 12 months and finally cleared up under treatment which consisted in the main of massage and dilatation at intervals of 1 to 3 weeks. Ten others had poor results requiring secondary resection and among these are included cases of re-contracture of the bladder neck following resection. Of 49 cases with glands larger than 20 gm., 40 (81 per cent) had good results and 9 were classified as fair and poor results. This gave an overall picture of 107 (81 per cent) as benefited and 32 (19 per cent) the same or worse after surgery. As stated previously, these patients continue to appear for further care and some of them complain for a long time of pain and frequency. These patients who continue to have symptoms frequently present negative cystoscopic findings and the prostatic urethra appears well resected.

It is interesting to note that the group with smaller glands gave a poorer functional result than the larger hypertrophies. It is commonly agreed that it is for the smaller glands that transurethral resection is best indicated.

RE-OPERATION

Of the 105 cases, 10 required a secondary resection while in the hospital, and 10 others re-entered the hospital for a secondary operation. Four of the 10 patients who were resected again while in the hospital were patients who had atonic and so-called "neurogenic bladders," in whom it is frequently not possible to determine whether enough tissue had been removed at the time of the first operation. The other 6 patients were individuals with large hypertrophies in whom not enough tissue could be removed at one sitting. The 10 patients who re-entered the hospital for a second operation presented either obstructive symptoms or considerable pain and burning in whom, on cystoscopy, it was noted that there was some tissue remaining in front of the veru or that the lateral lobes and the roof had not been well resected.

INCONTINENCE

Of these 150 patients, 2 showed temporary incontinence. In 1 case incontinence persisted for 3 months and in the other, for 1 year. Both finally cleared up completely and now have good control. We have been very careful when doing a resection not to cut distal to the verumontanum and we have therefore found that incontinence is not a problem with us if we observe this rule.

URETHRAL STRICTURE

Strictures at the meatus offer no great problem. They are somewhat annoying and the meatus requires repeated dilatation, yet can frequently but not always be avoided by a meatotomy which we do routinely if it is difficult to pass the instrument. Strictures in both the pendulous urethra and the membranous urethra are not uncommon, as all urologists are aware, as a sequel of transurethral resection. This often presents a rather serious problem for these patients continue to complain of urinary difficulty and require constant attention in many cases over a long period of time. Some of these strictures are almost filiform in caliber and require dilatation over a long period of time. The patient is not infrequently left with a stricture of the urethra which will permit passage only of a No. 18 to 20 sound. The stricture of the urethra is due, in the main, to over dilatation by the No. 28 instrument. The caliber of many urethras is often such as not to comfortably accommodate this sized instrument, and thus, tears occur with later scar formation and narrowing of the caliber of the urethra. Aside from the factor of over dilatation of the urethra with the resectoscope and the constant to and fro movement of the instrument during the operation causing some irritation and thereby promoting stricture, there is also another factor. The bakelite-sheath of the instrument may not be entirely a nonconductor of heat. When the resectoscope is removed at the end of the operation one usually finds that the sheath is dry. Attempts to overcome this by lubrication of the urethra and sheath with vaseline at the beginning of the operation have not proven very practicable with us. Urethritis and peri-urethritis frequently result with localized areas of narrowing and later stricture formation. We have had a few cases of chronic, diffuse infiltration of the urethra with narrowing of the urethra throughout almost its entire length. In these patients, a chronic chordee results, so that erection and coitus are interfered with. In order to prevent strictures due to possible over dilatation of a urethra of small caliber we have follwed the method recommended by Nesbit of inserting the resectoscope through an external urethrotomy. Although we have done many more, only three of the patients of this series had external urethrotomy. It is evident to us that a larger number should have received the benefit of an external urethrotomy. It can be concluded that some of these strictures following resection in this series were an avoidable complication.

BLADDER NECK CONTRACTURE AS A SEQUEL OF TRANSURETHRAL RESECTION

This has been our greatest problem and is the one complication that has concerned us and prompted the presentation of this paper. The operation of transurethral resection has been almost perfected through the years. There have been improvements in the cutting instruments, the optic mechanism, in technique and pre- and postoperative care. However, it would seem that the thermal effect upon the tissue by the electric cutting current has undesirable effects that have not been overcome or controlled. The depth of the thermal penetration of the current is greater than is generally appreciated and this is probably the cause of the contracture of the bladder neck which results later in some cases from the inflammatory reaction. We have had occasion to examine the bladder neck and prostatic urethra immediately after resection when extravasation had occurred and cystotomy was necessary. We have been impressed by the extreme leathery feel of the resected area, particularly after the use of the spark gap current. Although Weyrauch, Bassett and Berger believe that the spark gap coagulating current is far superior to that developed by a Bovie unit, our experience has been entirely the opposite. We are of the impression that the tube current does not produce as great thermal penetration as the spark gap. We agree with them that the coagulating currents are the most destructive and that in employing cutting currents the stroke should be as rapid as possible. We have had occasion to compare the tissue removed by the older spark gap coagulating current in the Bovie unit with that of the tube current employed in the newer instrument. The tissue removed by the coagulating spark gap current appears charred and gives the odor and appearance of burned tissue. The tube current makes a clean cut and the tissue does not look charred, with only a very slight odor of a burn.

We have had experience with immediate cystotomy for extravasation during transurethral resection in cases where the spark gap current had been used and also following the use of the tube current. In all cases where the spark gap coagulating current for cutting had been used the prostatic bed upon cystotomy was noted to be leathery in consistency, rather hot and dry. Where the tube current had been used the prostatic bed felt soft, almost as one would note after an open operation. We have had occasion to do cystotomy for the removal of either stone or tumor in the bladder on patients who previously had a transurethral resection. The bladder neck in these patients is frequently very hard and rigid and markedly fibrotic. In some cases the bladder neck is markedly contracted, occasionally almost pin-point. We have been in the habit of doing wide resection, in fact, so wide occasionally, that extravasation occurred in a few instances where it probably would not have, had we been less bold. However, despite this wide resection of the bladder neck for the relief of contracture, marked re-contracture of the bladder neck with sclerosis as a late result of the resection has been noted frequently enough to be disturbing.

We have operated upon large prostates transurethrally and have been satisfied after repeated trials that we can remove the large as well as the small prostate by this route. However, because some tissue was frequently left behind and second and third operations were necessary and hemorrhage as an aftermath occurred more frequently, we concluded that the large prostates could be best removed by us through an open operation. We have therefore limited ourselves, in most cases, during the past few years, when doing transurethral resection, to lesser degrees of glandular hypertrophy and bladder neck contractures.

It is, however, in these cases of bladder neck contracture for which transurethral resection is particularly indicated, that the distressing complication of recontracture occurs. Various transurethral procedures for removal of obstructions of the bladder neck have been recommended and employed for over 100 years since Guthrie first recommended it in 1837 for hypertrophy of the interureteric ridge. Contractures of the bladder neck are commonly seen in our older patients who frequently have complete urinary retention and the operation of transurethral resection offers them the best results. However, while the results are good in most cases, in others the end results are poor. Some of the poor results are due to later recontractures of the bladder neck. The symptoms of urinary frequency and discomfort which persist may also be due to the sclerosis of the trigonal muscle and prostatic bed as a late after effect of the thermal penetration. We have been very careful in choosing our patients for resection, no borderline or questionable cases of possible bladder neck obstruction were operated upon because these are the particular ones which give considerable trouble later and in whom the symptoms are markedly aggravated following the resection. Apparently one superimposes a burn or scar in these patients on the previously engorged and inflamed tissues.

It is interesting to note that these recontractures of the bladder neck nearly always follow resection of small prostates and contractures. Transurethral resections for large prostatic hypertrophy is rarely if ever followed by contracture of the bladder neck as a sequel. The question here arises whether the tendencies toward contracture are inherent in the tissues in which a bladder neck contracture had been present. It is also probable that the large prostatic bed and cavity which results from the resection of the large prostate even though it may contract somewhat postoperatively does not contract enough to narrow the bladder neck. We occasionally see patients who have been resected in whom it is not possible to pass a sound through the bladder neck because of the marked contracture, and who constantly present symptoms of frequency, urgency and dysuria. In some it has been possible to pass only a filiform with difficulty and then attach a small Le Forte sound or to pass only a small bougie into the bladder.

It is possible that it would be best to merely cut out a wedge from these contractures at the time of resection as is done in open operations rather than do a wide circular resection. Perhaps the prevention of this complication of bladder neck contracture following transurethral resection for relief of the same condition lies in the perfection of the tube current which produces much less charring of the tissue. Is it possible that the way to avoid this complication would be the use of the cold punch?

The end results of transurethral electroresection for bladder neck contracture and obstruction due to lesser degree of prostatic hypertrophy are satisfactory in most cases. It is quite unsatisfactory in an appreciable number of instances so that we may ask ourselves what can be done to improve it. In some cases frequency and dysuria persist without evidence of stricture or contracture of the bladder neck. Are these symptoms due to sclerosis of the prostatic bed as a late effect of thermal penetration? It may not be possible to avoid these occasional complications following electroresection for this may be due to an inherent fault in the operation from the effect of the current on the tissues.

RETROPUBIC PROSTATECTOMY

Before discussing the functional end results of retropubic prostatectomy we should like to mention two points in the technique of retropubic prostatectomy, both of which have been emphasized by Presman: 1) Elevation of the pelvis by the use of the kidney rest. This is placed at the level of the symphysis and raised to its maximum height. 2) Transverse abdominal incision. Both the elevation of the pubis and the transverse incision are of extreme value in facilitating the operation, thus allowing for more working space and excellent exposure of the prostate. Bleeding can be seen and controlled by suture and there is no trauma to the bones. The prostatic cavity can be best visualized in retropubic prostatectomy. One cannot see as well in perineal prostatectomy nor can the bladder neck be observed as well in either perineal or transvesical prostatectomy. Tags and small amounts of tissue and infected capsule can be removed under vision and one can inspect the prostatic cavity well. We have not found it necessary to employ the bag catheter nor should too great reliance by placed on it for when there is bleeding during the operation either in the capsule or at the bladder neck from which a wedge is cut routinely, only sutures will control. We are also impressed, paradoxical as it may seem, with the control of bleeding at the time of operation. As stated previously, one cannot depend upon bags or compression for the control of bleeding in this operation. In one of our early cases death resulted from bleeding from the anterior plexus which could not be controlled by either pack or bag. However, the bleeders can all be readily visualized, clamped and sutured and when that is done, the problem of control of bleeding is solved much better than in either of the three other operations: transurethral, suprapubic or perineal. Usually only a simple straight catheter is necessary for bladder drainage.

We have been remarkably impressed with our end results following retropubic prostatectomy. We have also been impressed with the smooth postoperative course these patients have. These patients have very little rise in temperature. They are usually up and about the next day after the operation. They get well quickly and urinate well postoperatively. The urine is crystal clear within a few weeks. Only following perineal prostatectomy is the urine as clear. The abdominal wall following the transverse incision is even more firm than it had been before operation. Two of our 24 patients developed slight tenderness near the symphysis pubis 4 weeks postoperatively, both of which cleared up after a period of 3 weeks. While these patients were slightly uncomfortable they were not disabled and presented neither clinical nor roentgenological evidence of osteitis pubis. We have had no cases of osteitis or periostitis pubis following retropubic prostatectomy except in our early Cook County Hospital cases; in fact the only case of periostitis pubis we have had in the past two years in our private practice followed suprapubic cystotomy.

The functional results in these 24 cases were uniformly good except for one patient in whom symptoms persisted and contracture occurred as a result of poor technique by us. He later required a transurethral resection of the contracture of the bladder neck and is now quite well. The operation of retropubic prostatectomy is not a simple procedure. However, if the urologist will take the pains to carry it out carefully, he will be gratified with satisfactory end results in frequently having a patient who is urinating freely with a clear urine and feeling well within 2 to 3 weeks postoperatively. Although this is the picture in many cases, complications and prolonged convalescence occur occasionally here as with the other operations.

The urine has remained cloudy for periods of 6 to 10 weeks. Secondary bleeding occurs occasionally. Two of the 24 patients required the use of the resectoscope in order to control late bleeding. Potency is not disturbed in most cases, although some patients have complained of its loss following retropubic operation.

However, the functional end results, as stated previously, have been almost uniformly good with this operation. The urine is clear very early, these patients do not continue to complain of frequency and the stream is good and remains good.

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RETROPUBIC, EXTRA-URETHRAL AND EXTRAVESICAL PROSTATECTOMY

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In 1933, Jacobs and Casper enucleated the lateral prostatic lobes retropubically through a longitudinal incision in the prostatic capsule, in an attempt to preserve the prostatic urethra. Had they continued along these surgical concepts, more extensive use of the retropubic procedure, and perhaps further modification, might have been realized during the following years.

With the advent of Terence Millin and his advocation of retropubic prostatectomy, there is increasing enthusiasm among many urologists for this method with each additional case performed. I find myself, after a series of over 200 cases, in complete accord with the claims of the many advantages to this method. I have been most fortunate in not encountering any immediate mortality or severe complications, such as secondary hemorrhage, fistula, infection of space of Retzius, osteitis pubis, or incontinence. Impotence has been present only in 2 cases of radical retropubic prostatectomy for prostatic carcinoma.

The functional results were very satisfying. In the course of this operative series, it was noted that the opening of the urethra in simple lateral lobe adenomas could be avoided. A series of 20 selected cases, therefore, was run to further develop this finding. Although such a short series has no particular statistical value, it has enabled me to effect a more deliberate technique.

Recently, A. E. Goldstein published a series of 36 cases of an extra-urethral and extravesical procedure by way of the perineal approach, with a lowered mortality and morbidity as compared with other perineal methods. Inasmuch as retropubic prostatectomy is considered by many as a perineal enucleation in reverse, it is apparent that the supposition to allow the urethra to remain intact, is possible, can be performed similarly in screened cases of lateral lobe enlargements with or without accessory lobes.

In the selection of the cases, the carcinomatous gland, the large intravesical intruding middle lobe, the subtrigonal median lobe, prostatic calculi, and previous transurethral resections were excluded, as the difficulty in preserving the urethra is apparent.

The most suitable cases for this procedure are the uncomplicated lateral lobe enlargements and small attached or unattached lobes with a minimal amount of bladder or prostatic infection. Cases with residual urine and deep bas-fond were not included. Excision of a wedge shaped piece of tissue from the floor of the vesical neck foregoes the preservation of the urethra.

The operation is performed following Millin's description. (A word picture study of the complete procedure is well illustrated in the case reports of Lowsley and Gentile.) The modification consists primarily of leaving the entire prostatic urethra intact while removing the lateral lobes and possible small attached or unattached median lobes. When the prostatic capsule is exposed, a No. 24 sound is passed into the bladder for identification of the urethral course, as well as lending assistance to immobilize the urethra and the encircling adenomatous prostate. A No. 24 soft rubber catheter can also be used, but the mobility of the prostatic urethra with the indwelling catheter delays the promptness of its identification.

After a suture ligature is placed both distally and proximally in the coursing venous plexus of Santorini, a transverse incision is made in the prostatic capsule, about 0.5 cm. from the prostatovesical junction. The incision is deepened on the lateral aspects of the capsule first, and then prolonged to the roof after the sound containing urethra has been identified and preserved. With digital aid as well as the enucleating end of a tonsil pillar retractor, the lateral lobes are developed, and the apex of the prostate can be observed. One lobe is removed at a time. Deliberate and careful sharp dissection, using a 9 inch long handle abdominal scissor at this point to separate the lateral lobes from the urethra, is essential. The urethral wall is very thin and buttonholing the tissue may occur with the attempt at removal of all tag tissue. No attempt is made to suture the openings. If a median lobe is present, the prostatic urethra is carefully retracted laterally. The vesical neck is pulled upward and laterally using an Allis clamp; and sharp dissection is carried out under the vesical neck or trigone to remove the adenoma. Bleeding following complete enucleation is not excessive; any observed ooze is controlled by the fulgurating current and on rare occasions using oxycel. The sound is removed and a No. 24 Foley 30 cc retention bag catheter is inserted into the bladder. The capsule is tightly closed with a continuous No. 1 chromic suture. A Penrose drain is carried over the line of suture and brought out at the upper end of the wound. The abdomen is closed in the usual manner.

TABLE 1. *Summary of cases*

CASES	AGE	PROSTATE		P. O. DAYS IN HOSPITAL	URETHRA
		WEIGHT	LOBES		
1	58	23	Bilobed	7	Intact
2	62	36	Bilobed	7	Intact
3	73	35	Bilobed	7	Two small openings
4	59	28	Bilobed	6	Intact
5	60	40	Bilobed	7	Intact
6	64	52	Trilobed	8	Partial removal
7	72	37	Bilobed	7	Intact
8	70	42	Bilobed	8	Longitudinal section remaining
9	81	38	Bilobed	8	Partial removal
10	56	46	Trilobed	7	Small opening
11	67	53	Trilobed	7	Intact
12	74	36	Bilobed	7	Intact
13	62	41	Bilobed	7	Intact
14	68	39	Bilobed	8	Two small openings
15	70	38	Bilobed	7	Small opening
16	76	43	Bilobed	7	Intact
17	66	50	Trilobed	7	Longitudinal section remaining
18	67	29	Bilobed	7	Intact
19	73	37	Bilobed	7	Intact
20	75	42	Bilobed	7	Intact

The catheter acts as a safety measure for any inadvertent urethral tears and to dispose of any clot formation. It is removed within three days and the patient allowed to void. The Penrose drain is shortened daily and is completely out on the fourth day.

The results in this short series overshadow any of the methods of open operation both as to length of hospital stay and lessened amount of complications (table 1). In those cases where no opening was made in the urethra, the hospital course was significantly smooth. Where the urethra was torn excessively, the operation could be likened to that of the Millin procedure with as much of the urethra allowed to remain as possible. In a few cases, a longitudinal section of the urethra was the only connecting tissue to the vesical neck.

The operation of preserving the urethra is much easier than anticipated, and the results obtained certainly warrant the added time in doing a more meticulous and deliberate procedure.

Although follow-up study on these cases covers only a 1-year period, the lack of any serious complicating features is noteworthy. The urethral canal, on cystoscopy, showed a uniform smoothness, and anatomical landmarks were more easily identified. There was less tortuosity in the posterior urethra. No residual urine in any of the cases was recorded. Postoperative bladder tolerance and capacity were infinitely better than in other procedures and infections cleared more rapidly. There was no incontinence from the time the catheter was removed and the patient allowed to void. Sexual potency was undisturbed.

The question of malignancy or recurrent adenomatous development from any remnant para-urethral gland inclusion may be offered in controversy to this modification. The incidence of this occurrence, however, is less than one per cent; and in the light of the lessened morbidity and rapid comfort found in this method of prostatic removal, it warrants preservation, if possible, rather than eradication.

SUMMARY

A modification of the retropubic prostatectomy with preservation of the urethra is offered in selected cases. The procedure consists of removing the lateral and small median adenomas by an extra-urethral and extravesical technique in screened cases of prostatic enlargement.

In the 20 cases performed, there were no complicating features, and hospital stay in any case did not exceed 8 days. In the other cases of retropubic prostatectomy, the results have been very gratifying, and I unhesitatingly urge others to devote their surgical ability along these lines.

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REFERENCES

Goldstein, A. E.: J. Urol., **57**: 1145–1157, 1947.
Jacobs, L. C. and Casper, E. J.: Urol. & Cutan. Rev., **37**: 729–732, 1933.
Lowsley, O. S. and Gentile, A.: J. Urol., **59**: 281–296, 1948.
Millin, T.: Proc. Roy. Soc. Med., **39**: 327–338, 1946.
Millin, T.: J. Urol., **59**: 267–274, 1948.

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OSTEITIS PUBIS

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ment and wide acceptance of retropubic prostatectomy, rare disease. The incidence of osteitis pubis following the 1 is so high that many urologists will not do the operation; o constitute the chief contraindication to the procedure. The s series has varied from zero to 10 per cent. We have had 3 bic operations.

he pathology and pathogenesis of this syndrome is still un- lamed injury to the periosteum of the pubis. This, however, he reported cases of osteitis following transurethral resection, th infection, prostatic abscess and the few instances in non- Many writers believe that infection in the prevesical space in- steum and/or bone is responsible. In some cases, infection has ed by the presence of a draining sinus. A few cases of actual h formation of sequestra have also been reported. On the other g and Vest, in 3 of their cases, explored the retropubic space and found no evidence of infection or periostitis. Kessler reported an autopsied case that showed bone atrophy, but no evidence of osteomyelitis. Wheeler pointed out the many features in common with Sudeck's bone atrophy. He rejected an inflammatory etiology on the following grounds:

1. In osteitis the process is widespread and there is extensive decalcification of bone. Periostitis is a more localized disease and deposits of cortical bone are frequent.
2. Osteitis heals with normal bone formation; no sequestra are formed. Osteomyelitis heals with formation of new bone and sequestra are the rule.
3. Osteitis is a self-limited disease. Osteomyelitis tends to recur and incomplete healing is frequent.

In an attempt to gain a better understanding of the mechanism involved, we have reviewed 31 cases of osteitis pubis and 2 cases of osteitis of the spine reported in the literature. These followed transurethral resection of the prostate in 8, two-stage suprapubic prostatectomy in 13, one-stage suprapubic prostatectomy in 4, retropubic prostatectomy in 4, abdominoperineal bowel resection for carcinoma in 1, bladder neck resection through a suprapubic approach in 1, perineal prostatectomy following a preliminary cystotomy in 1, ureterolithotomy in 1 and severe B. coli pyelonephritis, a nonoperative case, in 1. The latter 2 cases were females. Of the cases reviewed, 11 had a mild anemia. In 15 cases recorded, leukocytosis occurred ranging from 10,000 to 18,000 per cubic millimeter associated with increase in polymorphonuclear leukocytes. In 1 case two blood cultures showed B. coli. Urine cultures were reported in 15 cases. Organisms found included B. coli, B. proteus, B. pyocyaneus and Staphylococcus aureus. Microscopic examination of the urine reported in 7 cases revealed pus in all and erythrocytes in some. Fever up to 102 F was recorded in 13 cases and an afebrile course reported in 2. Radiographic changes of osteitis pubis were recorded in 26 patients, the earliest occurring 3 weeks following surgery, the latest after 24 weeks, but averaging 6 weeks. Acid and alkaline serum phosphatase reported in 6 cases were normal. Serum calcium and phosphorus were recorded in a few cases and were normal. Four cases had a draining, suprapubic sinus. Therapy in general was unsatisfactory. Antibiotics and the sulfonamides, separately, or in combination, had little effect although, in some instances, the acute phase was apparently somewhat relieved. Large amounts of vitamin B complex seemed of some value. Favorable response to prostigmin in some instances was noted. The results of diathermy and x-ray treatment were equivocal. Traction and casting helped to relieve the adductor spasm. By and large, the results as recorded were unsatisfactory and the patients underwent a prolonged convalescence. The longest total duration of symptoms was 9 months, the shortest 7 days and the average 3.5 months.

There are several important features common to all the cases reviewed:

1. Infection of varying severity seemed to be a factor in all cases adequately studied. However, the response to antibacterial therapy was poor and the syndrome persisted for a variable period of time after apparently all infection had been cleared.

2. The symptoms, usually sudden in onset, began weeks or months after the operation.

3. Although occasional cases with true osteomyelitis of the os pubis have been reported, the pathological process in most seems to have been a bone atrophy and not an inflammatory process.

From this we have drawn the following tentative conclusions:

1. Two different diseases of the os pubis must be distinguished; namely, osteomyelitis, a rare condition which is not different from osteomyelitis in other bones, and osteitis pubis which is a bone atrophy and not an inflammatory process.

2. Since infection in the space of Retzius or elsewhere in the pelvis is apparently present in all cases of osteitis pubis at some time, it appears likely that some connection exists between this infection and the bone atrophy.

We agree with Wheeler's viewpoint and believe that a mechanism similar to the one causing Sudeck's atrophy is involved in osteitis pubis. It appears probable that a chronic inflammatory process within the pelvis may produce irritation of sensory nerves which, through a causalgia-like mechanism, leads to pain, ischemia, muscle spasm, and trophic changes. The delayed and usually sudden onset of the symptoms is in agreement with this theory. An acute inflammation of relatively short duration is not likely to produce chronic nerve irritation. But a chronic, though low-grade inflammation may cause continuous nerve irritation, partly by metabolites and partly mechanically by formation of scar tissue. If the nerve irritation reaches a certain intensity, it may suddenly manifest itself by a causalgic spread of reflexes; or if the nerve irritation was insufficient to produce the full-blown picture of osteitis, it may have a "sensitizing" effect so that any additional stimulus such as straining while getting out of bed may act as a trigger mechanism and precipitate a causalgic process. A point requiring clarification is the question of why osteitis pubis develops more frequently after operations on the prostate than after other, similar operations in the same area, for example after cystotomy; and why it is so much more common after retropubic operations than after the other types of prostatectomy. The answer is that a causalgic process is most likely to develop if an irritative lesion affects a concentration of nerves. The prostate and its capsule are known to have a very rich sensory nerve supply and, therefore, the prostate is more likely to become the origin of a causalgia than the adjacent tissues and viscera. It is a common experience that patients who have undergone a prostatectomy of any type may develop backache, sciatica, fibrositis and arthritis weeks or months after the operation. Since such symptoms are not rare in patients of this age group, the connection with the operation is not recognized. The symptoms are usually or predominantly referred to the back and to the posterior aspects of the lower extremities and this, we believe, is due to the fact that in most types of prostatectomy the trauma and inflammation involve mainly the posterior and lateral lobes of the prostate. This would explain the recently reported cases of osteitis of the spine after prostatectomy. But if the trauma, infection and scarring involve the anterior surface of the prostatic capsule, the pain and reflexes will be referred anteriorly to the pubic and adductor regions. Since in a retropubic prostatectomy the anterior surface of the prostatic capsule is incised, this operation is more likely to be followed by osteitis pubis.

Successful treatment depends on two factors. The first is removal of the focus of irritation which, in our cases, was infection. Secondly, since removal of the original focus does not necessarily lead to interruption of the noxious reflex, the reflex itself may have to be eliminated. Clearing of an infectious process in the periprostatic tissues and prostatic capsule is difficult to achieve by the usual systemic administration of antibiotics and sulfonamides because of the presence of scar tissue and a compromised blood supply. To bring the antibiotics into more direct contact with the infected area, topical application of the various antibiotics in combination with a diffusing agent is useful. This technique was suggested by the work of Grace in treating chronic osteomyelitis. We have used an aqueous solution of zephiran chloride, but other detergents and perhaps hyaluronidase may be equally suitable. If infection alone is the responsible irritating factor, its eventual clearing should produce a clinical cure. If the symptoms persist in spite of apparent clearing of the inflammatory process, the next objective should be the interruption of the pathologic reflexes. As in causalgias in general, relief should be expected from sympathetic block or from novocaine block of the trigger point. The following cases illustrate the clinical application of these principles:

CASE REPORTS

Case 1. A. L., a 66 year old man, was admitted to Charles S. Wilson Memorial Hospital, May 13, 1948 with acute urinary retention. A one-stage suprapubic prostatectomy had been done elsewhere 6 months previously. The gland was large and fibrous. Convalescence had been satisfactory until an episode of chills and fever occurred on the twelfth postoperative day. The temperature returned to normal within a week and the patient was discharged. Two weeks later pain developed in the pubic region and back. One month after discharge he was admitted with urinary obstruction and a transurethral resection was performed. After discharge the patient was treated with urethral dilatations at regular intervals. However, urination continued to be somewhat difficult and the pain in the pubis and back persisted so that the patient was scarcely able to walk. When first seen by one of us (E. F. H.), the patient walked with great difficulty, bent over to nearly 90 degrees and using 2 canes. Examination revealed a stricture of the prostatic urethra which, after some difficulty, was passed with a filiform sound. The urethra was dilated with followers and indwelling catheters up to 22 F over an 8 day period. The patient was then able to void with ease, but there was no change in his pain or ability to walk. Cystoscopy on May 25, 1948 showed patches of inflamed bladder nucosa. In the posterior urethra, about 1 cm. behind the verumontanum there were fuzzy, necrotic tags of prostatic tissue. In the vesical neck region the urethra appeared smooth, pale and indurated. Six cubic centimeters of 1 per cent novocaine solution was injected into the prostatic capsule in the region of the tags and into the vesical neck. The area was densely scarred and much pressure was required to accomplish the infiltration. Within a few minutes the patient stated that the ache in his back and sides had decreased considerably and he was able to walk around the room slowly, in erect posture, with comparatively little discomfort without using a cane. Three days later he reported continued improvement and when last seen, 10 months later, felt well and had had no pain since the injection. No radiographs were made on this patient, but the symptoms and physical findings were consistent with a diagnosis of osteitis.

Case 2. P. F., a 76 year old white man, was admitted to Charles S. Wilson Memorial Hospital on December 9, 1948 with acute urinary retention. The prostate was 3 plus enlarged and there was a hard area on the left side of the apex. A diagnosis of adenoma and probable carcinoma was made. Serum acid phosphatase was 0.5 Bodansky units. Urine culture was sterile. Because of the patient's age and poor general condition, radical prostatectomy seemed contraindicated. Retropubic prostatectomy and bilateral orchiectomy were done on December 17, 1948. On the second postoperative day, the temperature rose to 104 F, was normal by the seventh day, but rose again slightly and persisted. Penicillin and streptomycin were started on the first and second days respectively. By the fourth week the patient began to complain of pain in the pubic region which was aggravated by coughing. Adductor spasm developed and a suprapubic sinus about 2 cm. deep drained a small amount of purulent material. Radiograph of the pelvis showed no bony changes. The possibility that the draining sinus was the source of the irritation producing these symptoms through a causalgic mechanism was considered. Therefore $\frac{1}{4}$ per cent nupercaine solution was injected into the sinus. Thirty minutes later the pain had eased somewhat. Two hours later the patient could abduct his thighs more widely and the symphysis was only slightly tender to pressure. About 8 hours later all symptoms returned with about the original intensity. Nupercaine instillations into the sinus were repeated on several consecutive days with varying results. Because this procedure did not produce persistent relief, it was decided to try blocking the sympathetic nerves in view of their possible role in producing these symptoms. Etamon, 300 mg., was given intravenously and within 5 minutes the patient reported some relief of spasm and tenderness. However, a few hours later the symptoms recurred. Etamon in the same dosage was repeated on two more occasions. There was some improvement, but it was only temporary and, on some days, a similar improvement occurred spontaneously. In order to eliminate possible psychic factors as the basis for the patient's relief, normal saline was given intravenously. The effect was similar to that following etamon. Etamon apparently had no appreciable effect on the process. Continued drainage from the sinus indicated persistence of infection. Therefore, local therapy was attempted according to the method of Grace. A snugly fitting catheter was inserted into the sinus and a solution consisting of aqueous zephiran hydrochloride 1:1.000, 50 cc, furacin soluble 50 cc, penicillin 100,000 units, streptomycin 1.0 gm., allowed to drip in continuously and very slowly. After 6 days the treatment was discontinued and the sinus closed a few days later. Some diminution of spasm and tenderness followed with general subjective improvement, but there was still considerable painful residual muscle spasm and pubic tenderness. Since the sinus was closed and the infection had apparently cleared, the muscle spasm itself was considered a possible factor in producing the causalgic process. Therefore, 60 units of D-tubocurarine was given intravenously over a period of 10 minutes. Diminution of the muscular power in the arms and legs followed, but the local tenderness over the pubis was not changed. There was questionable lessening of the adductor spasm. By the following day the spasm had returned. Since all previous attempts to relieve the symptoms had failed, it was decided to block the presumptive trigger point, namely, the prostatic capsule. On the fifty-second postoperative day 15 cc of 1 per cent novocaine solution was injected into the anterior part of the prostatic capsule. Five minutes later the patient experienced little pain over the symphysis and pressure on the pubis produced little discomfort. The adductor spasm, which had been very marked before the injection, disappeared. The patient could sit up without pain and walk about the room with ease. Three days later he was ambulatory without complaints and was discharged. When he was seen 9 days after the injection he was complaining of moderate pain in the pubis apparently due to increased activity. There was practically no tenderness over the pubis, but some adductor spasm was present. After instillation of $\frac{1}{4}$ per cent nupercaine solution into the bladder and passing a 24 F sound, there was some relaxation of the spasm. One week later he had no tenderness over the pubis and the adductor spasm had considerably lessened. The patient died 2 months later, apparently due to a heart condition, but evidently had had no further complaints referable to the osteitis pubis.

Case 3. M. C., a 71 year old white man, was admitted to Charles S. Wilson Memorial Hospital on July 6, 1949 with acute urinary retention. The prostate was enlarged 2 to 3 plus, smooth and of elastic consistency. Urine culture was sterile. On July 19, 1949, retropubic prostatectomy and bilateral vasectomy were done. The following day the wound drained profusely and the odor of Pyocyaneus infection was noted. Chloromycetin 3 gm. daily by mouth was started and boric acid powder applied to the wound. The temperature returned to normal over a 5 day period. Catheter and prevesical drains were removed on the fourth postoperative day. The drainage from the wound was moderate and the sinus seemed to heal satisfactorily. On the tenth postoperative day there was some separation of the wound edges and a moderate amount of purulent drainage escaped. The patient, however, was ambulatory without complaints and was discharged. He was re-admitted 30 days after the operation complaining of pain along the medial aspects of both thighs becoming progressively worse, associated with pain on walking and great difficulty in getting in and out of bed. There was marked tenderness over the symphysis and spasm of the adductor muscles of the thighs. The suprapubic wound was well healed. Urine culture yielded a heavy growth of B. pyocyaneus and a few gram negative cocci. The patient was placed on chloromycetin 3.0 gm. daily and combisul TD 3.0 gm. daily. During the subsequent 4 days the urine cleared considerably, but there was only slight subjective improvement. A radiograph of the pelvis showed no bony changes. Since the urine had cleared sufficiently by the fifth day, a panendoscope was passed and the prostatic capsule injected with 31 cc of a 1 per cent novocaine solution containing 200,000 units of penicillin, mostly into the anterior capsule. Fifteen minutes later the patient could abduct his thighs practically to normal range and was able to get in and out of bed without lifting his legs with his hands. There was no pain in the pubic region and only very slight tenderness over the left ischium. Three hours later he was able to walk about the room in a normal manner. Two days later he was discharged without complaints. There was no pubic tenderness and he was able to abduct his thighs and walk with ease. Three weeks after discharge the patient reported by telephone that pain had not recurred. Further follow-up was not possible.

Case 4. L. J., a 62 year old white man, was first seen by one of us (E. F. H.) on October 11, 1948 with symptoms of prostatism. The prostate was 2 plus enlarged with an area of increased density in the left lobe. Acid and alkaline serum phosphatase determinations were within normal limits. Of two prostatic smears, one showed tumor cells. A diagnosis of carcinoma of the prostate was made and a radical retropubic prostatectomy performed on February 20, 1949. The immediate postoperative course was uneventful. The temperature was normal by the fifth day. On the tenth postoperative day, the patient complained of pain in the left ischium when sitting and both pubic bones were somewhat tender to pressure. By the twenty-fourth postoperative day, the clinical picture of osteitis pubis was definite. A radiograph of the pelvis showed no bony changes. There was still some drainage from the lower end of the abdominal wound. Repeated urine cultures yielded a mixed flora with B. pyocyaneus predominating. Beginning on the twenty-fourth postoperative day vitamin B complex intravenously and diathermy to the pubis were given daily for 6 days. There was a moderate, but transient relief of symptoms. On the twenty-seventh postoperative day 30 cc of a $\frac{1}{4}$ per cent nupercaine solution was instilled into the bladder. Fifty minutes later the adductor spasm had lessened and the patient was able to walk more easily and with less pain. He also noticed that coughing was not painful. Twenty hours later the symptoms were as severe as before.

Urinalyses showed varying amounts of pus and repeated cultures revealed the persistence of the organisms previously noted. At this time combisul TD, 3.0 gm. daily was started. On the thirty-fifth postoperative day, a urethrogram revealed a sinus tract (fig. 1) extending from the urethra to the left side of the base of the bladder, presumably in the region of the urethrovesical anastomosis. Since the patient was incontinent, it appeared probable that the pus in the urine came from the sinus which led into the infected perivesical space. This was assumed to be the source of the nerve irritation responsible for the symptoms. Passage of a ureteral catheter by means of a panendoscope into the perivesical sinus to inject a solution of zephiran chloride and antibiotics was considered. Before resorting to this, however, streptomycin 1.5 gm. daily was started and after 6 days the patient felt so much improved that he was able to be ambulatory. Therefore, the plan to treat the infection topically was abandoned. A radiograph on the fifty-third postoperative day still showed no bony changes. Urine cultures still yielded B. pyocyaneus. Streptomycin was discontinued after 7 days. Four days later the patient reported very little pain or discomfort and was discharged. Three weeks after discharge he still complained of some pain along the inner aspect of the left thigh and left side of the back. Instillation of nupercaine solution into the bladder gave some relief of muscle spasticity. Six months after the operation there was no tenderness over the pubis, but the patient complained of mild, sciatic pain on the left side, usually at night.

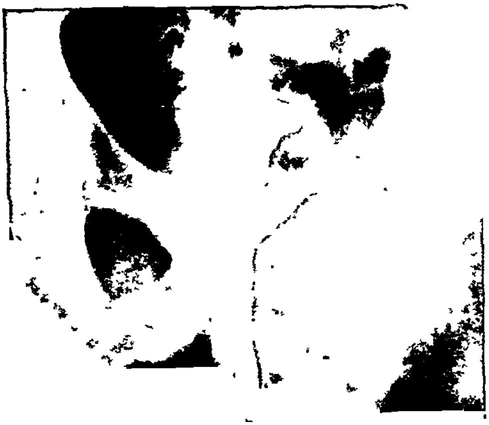

Fig. 1

COMMENT

Our case reports seem to indicate that our concept of the pathogenesis of osteitis pubis is basically correct. Case 2 is instructive in that instillation of an anesthetic into the suprapubic sinus, sympathetic block with etamon and curare failed to alter the course of the disease. The prompt response to novocaine infiltration of the prostatic capsule strongly suggests that the latter was the trigger point which produced the symptoms. On the other hand, case 4 demonstrates that the prostatic capsule cannot be the exclusive possible trigger point since in this patient the entire prostate including the seminal vesicles and ampullae of the vasa deferentia had been removed. The main problem in the management of osteitis pubis seems to lie in the elimination of the pelvic infection. Prevention of infection can be attempted, but will be difficult to achieve because the urine and prostate are already infected in many operative patients. The infection may be abated by antibiotics administered systemically if the antibiotics have access to the infected area. This seems to have happened in case 4 since a communication could be demonstrated between the urethrovesical junction and the perivesical sinus. In most cases systemically administered antibiotics will fail to reach the infected area and topical application by Grace's technique or a modification of it will be necessary. The technique is simple if there is a suprapubic draining sinus. In a case without a sinus, but in which an infected pocket in the retropubic space is suspected, one could aspirate through a needle, leave the needle in place and let the solution drip through it into the infected area; or insert an ureteral catheter through the needle and remove the needle. The composition of the sterilizing solution will also be subject to modifications depending on the bacteriology and the availability of new antibiotics.

Our experience with the treatment of osteitis pubis is limited and also the disease seems to have been less severe in our patients than in those observed by other writers since in none of our cases could changes in the pelvic bones be demonstrated by repeated radiographs. Further studies of this method in patients with extensive bone atrophy will be necessary to determine the effect in those cases.

SUMMARY

Previous concepts of the nature of osteitis pubis and of the various forms of therapy have been discussed.

Thirty-one cases of osteitis pubis and 2 cases of osteitis of the spine reported in the literature have been reviewed.

An attempt has been made to explain the pathogenesis of osteitis pubis on the basis of a causalgic process originating from chronic inflammation within the pelvis. This viewpoint is in agreement with Wheeler's theory.

A new method of the treatment of osteitis pubis has been outlined.

To support these new concepts of etiology and treatment four cases of osteitis pubis have been reported and their treatment discussed.

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REFERENCES

Abrams, M., Sedlezky, I. and Stearns, D. B.: New Eng. J. Med., **240**: 637, 1949.
Beer, E.: J. Urol., **20**: 233, 1928.
Bruskewitz, H. W. and Ewell, G. E.: Am. J. Surg., **77**: 705, 1949.
Cohen, H. H.: J. Urol., **55**: 84, 1946.
Donahue, C. D.: J. Urol., **61**: 405, 1949.
Grace, E. J. and Bryson, U.: New York State J. Med., **47**: 2204, 1947.
Hock, E.: Urol. & Cutan. Rev., **53**: 149, 1949.
Kleinberg, S.: J. Urol., **48**: 635, 1942.
Lavalle, L. L. and Hamm, F. C.: J. Urol., **61**: 83, 1949.
Lazarus, J. A.: Ann. Surg., **103**: 310, 1936.
Livingston, W. K.: Pain Mechanisms. New York: Macmillan, 1944.
Muschat, M.: J. Urol., **54**: 447, 1945.
Pottenger, F. M.: Symptoms of Visceral Disease. St. Louis: C. V. Mosby Co., 1944.
Rosenberg, M. L. and Vest, S. A.: J. Urol., **60**: 767, 1948.
Wheeler, W. K.: J. Urol., **45**: 467, 1941.

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FLAQUÉ-LOWSLEY OPERATION FOR URINARY INCONTINENCE: PRELIMINARY REPORT

ALBERT VERGÉS-FLAQUÉ

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The purpose of this paper is to present a new operation for the cure of urinary incontinence of non-neurological origin in the male, and to report the results in 7 clinical cases.

This form of incontinence is becoming a more common condition as time goes on, due partly to the increased number of prostatectomies that are being done. It is our impression that the most frequent cause is the too energetic application of the transurethral resectoscope, and that this is a type of incontinence particularly difficult to cure because of the rigidity of the urethra due to excessive scar formation. It is a fact, however, that urinary incontinence may follow any type of prostatectomy: suprapubic, retropubic, perineal, or transurethral.

Many cases of postprostatectomy incontinence can be cured by muscular exercise by the patient, as pointed out in an earlier paper.[1] However, after a suitable period of attempts to control the incontinence by this palliative means, without success, the patient should be considered a proper case for the application of the operation described here.

In this operation, the external anal sphincter is utilized as a substitute for the external urethral spincter when the latter is functionless. Embryologically, these two sphincters have a common origin—the cloacal sphincter. Both are supplied by branches of the pudendal nerve, both are made up of striated muscle fibers, and both have the same function, namely, retaining and allowing the expulsion of products of excretion. The external anal sphincter is, therefore, the logical muscle to utilize in place of the functionless external urethral sphincter.

EXPERIMENTAL WORK

The operation presented here was first performed on dogs. Nine animals were used. In the first 4 animals, two-thirds of the external anal sphincter was looped over the separated urethra. The result was a satisfactorily tight sphincter, and in 3 cases there were no complications. In the fourth case, there was fibrosis of the utilized portion of the anal sphincter. In 5 animals, the urethra was cut across and drawn under two-thirds of the external anal sphincter in situ, the cut ends of the urethra being then sutured together over an indwelling polyethylene catheter. One of the animals upon which this latter operation was done developed a urethroperineal fistula and 2 developed urethroperineal fistula and perineal abscess. This procedure was, therefore, abandoned in favor of the first operation (table 1).

Fifteen human cadavers were then operated upon, and it was found anatom-

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Read at annual meeting, American Urological Association, Washington, D. C., May 29, 1950.

[1] Vergés-Flaqué, A.: J. Urol., 61: 96, 1949.

ically feasible to insert two-thirds of the external anal sphincter around the isolated bulbous portion of the urethra, without excessive tension.

DESCRIPTION OF OPERATION

Preoperative preparation. The patient is given 45 cc castor oil the morning before the operation, and in the evening cleansing enemas until clear. For 24 hours preoperatively he is given chemotherapy and antibiotics and a liquid diet. The night before operation, nembutal, 0.1 gm. is administered.

TABLE 1. *Animal experiments*

DOG	TYPE OF OPERATION	SACRIFICED	DIED	AUTOPSY FINDINGS
1	Anal sphincter incised; looped over mobilized urethra	17 days		Sphincter well healed
2	Anal sphincter incised; looped over mobilized urethra	16 days		Fibrosis of sphincter
3	Anal sphincter incised; looped over mobilized urethra	5 mos.		Well healed
4	Anal sphincter incised; looped over mobilized urethra	5 mos.		Well healed
5	Urethra incised; drawn under anal sphincter in situ and anastomosed	35 days		Urethroperineal fistula
6	Urethra incised; drawn under anal sphincter in situ and anastomosed		1 day	Bronchopneumonia
7	Urethra incised; drawn under anal sphincter in situ and anastomosed	4 days		Urethroperineal fistula, perineal abscess
8	Urethra incised; drawn under anal sphincter in situ and anastomosed		1 day	Bronchopneumonia
9	Urethra incised; drawn under anal sphincter in situ and anastomosed	6 days		Urethroperineal fistula, perineal abscess

On the morning of operation he is again given cleansing enemas until clear. One hour before operation, nembutal, 0.1 gm., morphine sulphate, 0.015 gm., and atropine sulphate, 0.4 mg., are administered.

Technique. The patient, properly anesthetized, is placed in the lithotomy position. A 20F Foley catheter is inserted through the urethra into the bladder. (Dr. Lowsley uses the Lowsley long, curved prostatic tractor.)

An inverted-Y incision is made, with the vertical stem of the incision extending from the perineoscrotal junction to a point about 2 cm. above the anus, and the curved branches extending half-way around the anus (fig. 1, *1*). This is deepened through the subcutaneous fat and fascia, and the rectal sphincter is exposed.

The anterior circumference of the anal sphincter is isolated by sharp and blunt dissection and the central tendon divided (fig. 1, *2 to 5;* fig. 2, *1*). The separated anal sphincter is then divided into two parts along the fibers, the distal half being preserved for anal control (fig. 2, *2 and 3;* fig. 3, *1 and 2*).

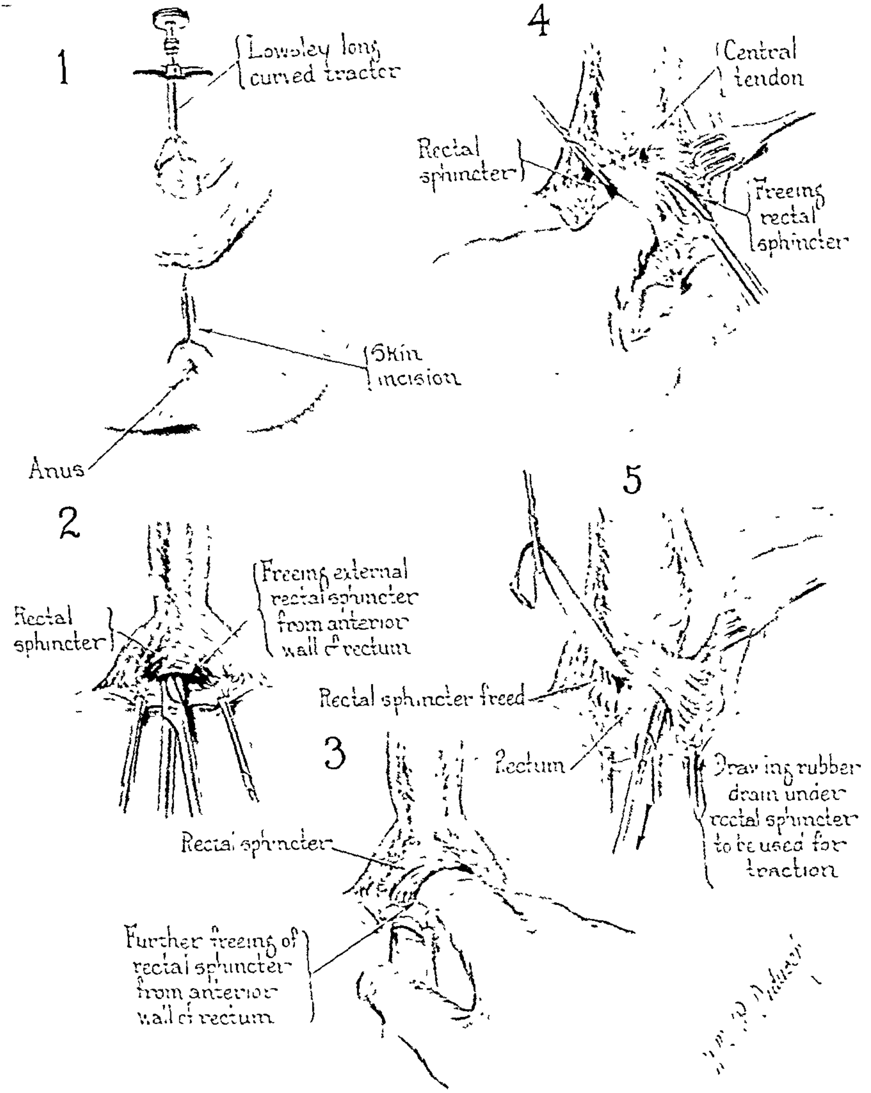
1
Lowsley long curved tractor
Skin incision
Anus
4
Central tendon
Rectal sphincter
Freeing rectal sphincter
2
Rectal sphincter
Freeing external rectal sphincter from anterior wall of rectum
5
Rectal sphincter freed
Rectum
Drawing rubber drain under rectal sphincter to be used for traction
3
Rectal sphincter
Further freeing of rectal sphincter from anterior wall of rectum

FIG. 1. Flaqué-Lowsley operation for urinary incontinence. *1.* Skin incision. (The author uses a 20F Foley catheter in place of the Lowsley tractor.) *2, 3, 4,* Freeing rectal sphincter from anterior wall of rectum. *5,* Drawing rubber drain, to be used for traction, under rectal sphincter which has been freed from anterior rectal wall.

Colles' fascia then is incised and the bulbous urethra isolated. If it can be done without difficulty, it is well to isolate a rather sizable portion of the urethra (figs. 3 and 4).

ically feasible to insert two-thirds of the external anal sphincter around the isolated bulbous portion of the urethra, without excessive tension.

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4	Anal sphincter incised; looped over mobilized urethra	5 mos.		Well healed
5	Urethra incised; drawn under anal sphincter in situ and anastomosed	35 days		Urethroperineal fistula
6	Urethra incised; drawn under anal sphincter in situ and anastomosed		1 day	Bronchopneumonia
7	Urethra incised; drawn under anal sphincter in situ and anastomosed	4 days		Urethroperineal fistula, perineal abscess
8	Urethra incised; drawn under anal sphincter in situ and anastomosed		1 day	Bronchopneumonia
9	Urethra incised; drawn under anal sphincter in situ and anastomosed	6 days		Urethroperineal fistula. perineal abscess

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The anterior circumference of the anal sphincter is isolated by sharp and blunt dissection and the central tendon divided (fig. 1, *2 to 5;* fig. 2, *1*). The

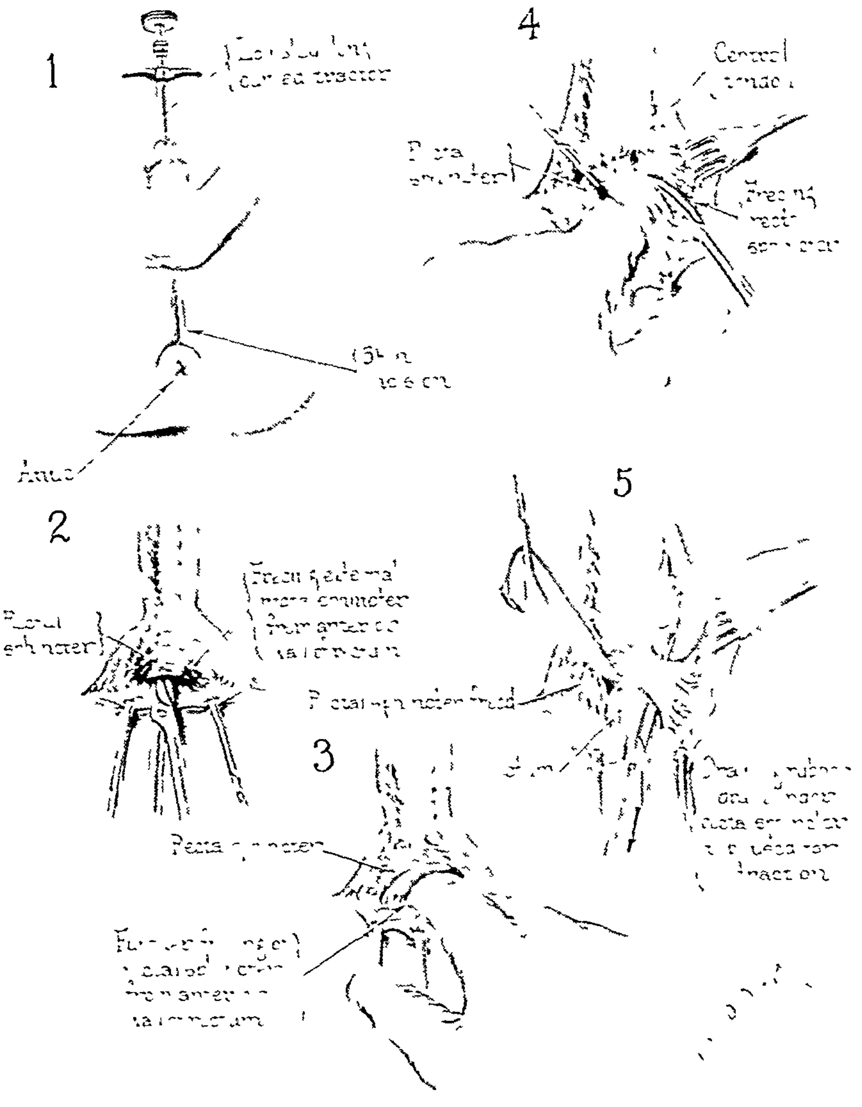

FIG. 1. Flaqué-Lowsley operation for urinary incontinence. *1.* Skin incision. (The author uses a 20F Foley catheter in place of the Lowsley tractor.) *2, 3, 4,* Freeing rectal sphincter from anterior wall of rectum *5,* Drawing rubber drain, to be used for traction, under rectal sphincter which has been freed from anterior rectal wall

separated anal sphincter is then divided into two parts along the fibers, the distal half being preserved for anal control (fig. 2, *2 and 3;* fig. 3, *1 and 2*).

Colles' fascia then is incised and the bulbous urethra isolated. If it can be done without difficulty, it is well to isolate a rather sizable portion of the urethra (figs. 3 and 4).

The portion of the isolated anal sphincter which is to be utilized in the operation is then incised, usually as far down on the left as is convenient (fig. 4, *3*). This muscle is then drawn around the isolated bulbous urethra and the cut end

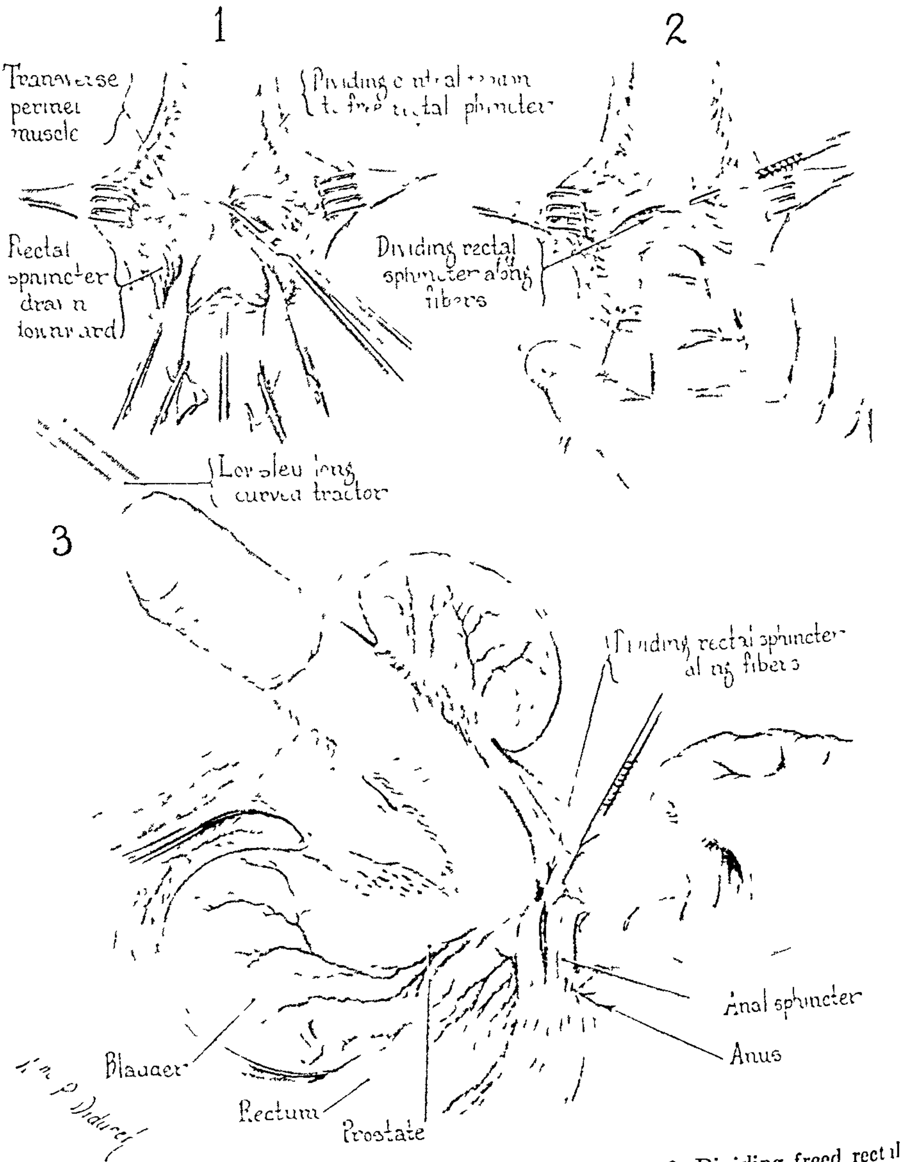
1
2
Transverse perineal muscle
Dividing central tendon to free rectal sphincter
Rectal sphincter drawn downward
Dividing rectal sphincter along fibers
Lowsley long curved tractor
3
Dividing rectal sphincter along fibers
Anal sphincter
Anus
Bladder
Rectum
Prostate

FIG. 2. *1*, Dividing central tendon to free rectal sphincter. *2*, Dividing freed rectal sphincter into two parts along its fibers (distal half preserved for anal control). *3*, Sagittal view of divided rectal sphincter.

sutured in its original position by two or more sutures of ribbon gut, causing a looping of the urethra (fig 5, *3*). Ribbon gut is an excellent material to use in fixing the muscle back in position because it does not tear through the delicate fibers. The author, however, has also used silk with success. Before the muscle is sutured back into its original position, a 16F soft rubber catheter must be inserted into the urethra because after the loop has been established catheterization is difficult. (The Foley catheter or Lowsley tractor is, of course, first removed.)

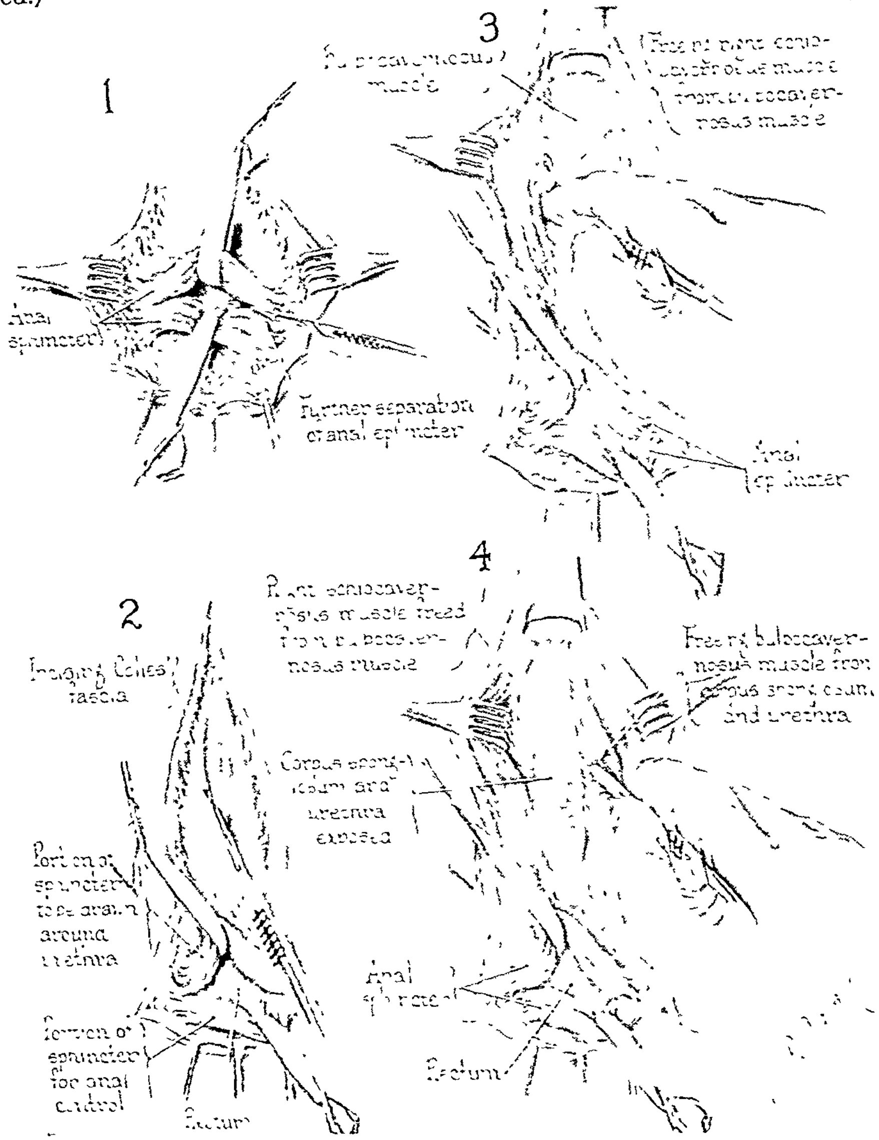
1
Anal sphincter
Further separation of anal sphincter
3
Bulbocavernosus muscle
Freeing right ischiocavernosus muscle from bulbocavernosus muscle
Anal sphincter
2
Incising Colles' fascia
Portion of sphincter to be drawn around urethra
Portion of sphincter for anal control
Rectum
4
Right ischiocavernosus muscle freed from bulbocavernosus muscle
Freeing bulbocavernosus muscle from corpus spongiosum and urethra
Corpus spongiosum and urethra exposed
Anal sphincter
Rectum

FIG. 3. *1*, Further division of rectal sphincter along its fibers. *2*, Sphincter divided into bundles. Incising Colles' fascia. *3*, *4*, Isolating bulbous portion of urethra.

The wound is closed in layers, a small amount of sulfanilamide powder being sprinkled into it (fig. 6, *1 and 3*).

The portion of the anal sphincter left for anal control is not interfered with in any way whatsoever, but is merely allowed to drop back into position.

Postoperative care. Postoperatively, the patient is given paregoric, 4 cc daily, for 5 days; chemotherapy and antibiotics, and a liquid diet for 3 days followed by a low residue soft diet for 3 days. The Penrose drain is removed gradually on the second and third days. The urethral catheter is kept on free drainage and removed (usually) between the fifth and tenth days.

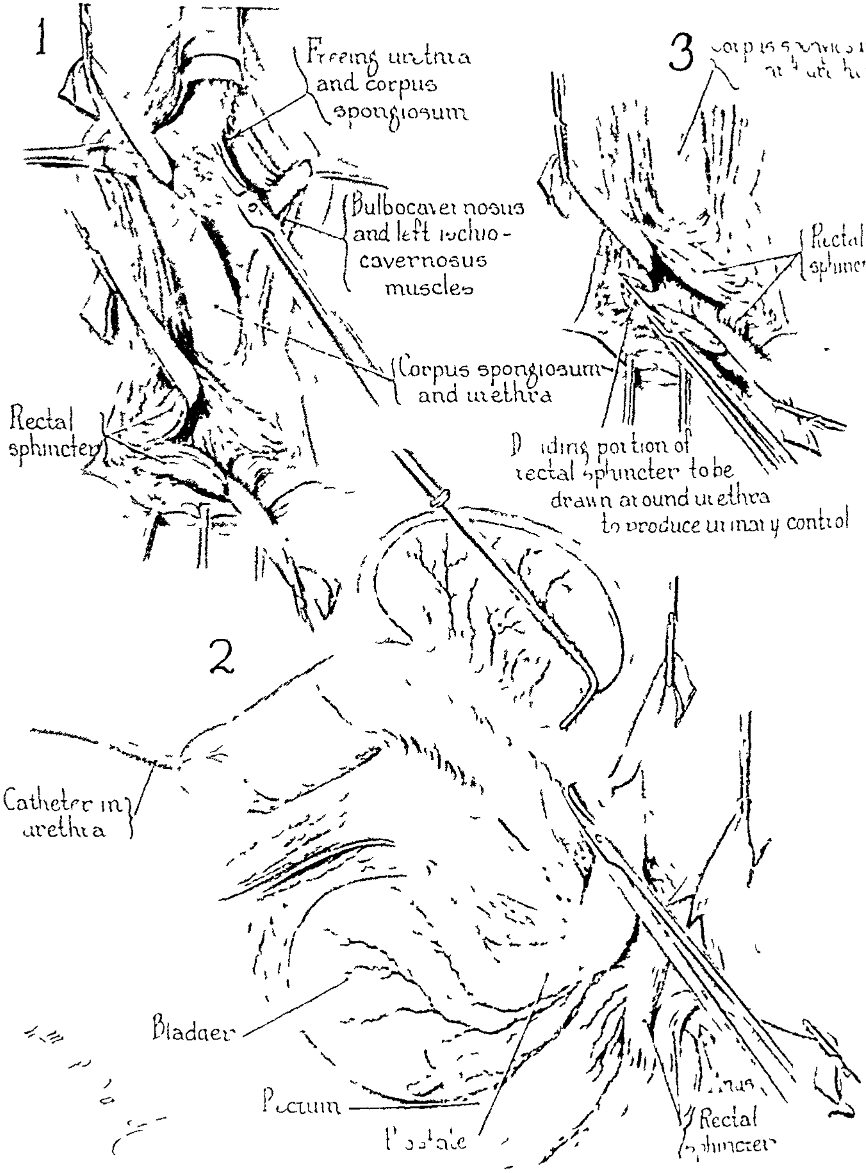
1
Freeing urethra and corpus spongiosum
Bulbocavernosus and left ischiocavernosus muscles
Corpus spongiosum and urethra
Rectal sphincter
3
Corpus spongiosum and urethra
Rectal sphincter
Dividing portion of rectal sphincter to be drawn around urethra to produce urinary control
2
Catheter in urethra
Bladder
Rectum
Prostate
Anus
Rectal sphincter

FIG. 4. *1*, Freeing of bulbous urethra continued. *2*, Sagittal view showing freeing of corpus cavernosum and bulbous urethra. (Lowsley tractor, or Foley catheter, has been replaced by 16F soft rubber catheter.) *3*, Dividing portion of rectal sphincter to be drawn around urethra to produce urinary control.

Two to three weeks postoperatively, exercises directed to starting and stopping the urinary stream by relaxing and contracting the anus are commenced and are continued until control of urination is satisfactory. The purpose of these exercises is to train the patient to make proper use of the anal sphincter and adapt it to its new dual function.

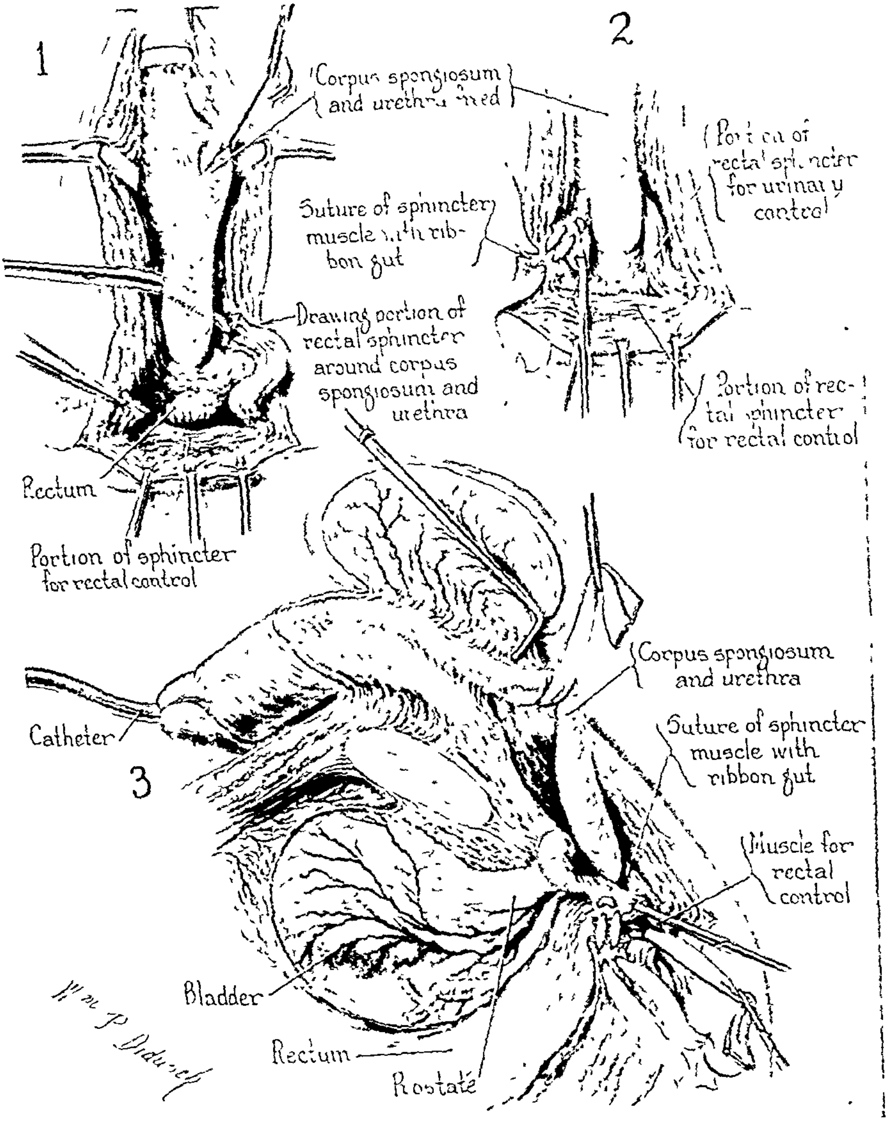
1
2
3
Corpus spongiosum and urethra freed
Portion of rectal sphincter for urinary control
Suture of sphincter muscle with ribbon gut
Drawing portion of rectal sphincter around corpus spongiosum and urethra
Portion of rectal sphincter for rectal control
Rectum
Portion of sphincter for rectal control
Corpus spongiosum and urethra
Catheter
Suture of sphincter muscle with ribbon gut
Muscle for rectal control
Bladder
Rectum
Prostate
Wm P Didusch

Fig 5 *1*, Drawing rectal sphincter around freed bulbous portion of urethra. *2*, Suturing cut end of sphincter in its original position with ribbon gut. (The author also uses silk.) *3*, Sagittal view showing suture of portion of rectal sphincter drawn around urethra.

REPORT OF CASES

Since June 22, 1949, when the operation was first performed clinically, 7 patients have been operated upon by this method (table 2). Their ages ranged from 43 to 67 years. Five had total and 2 partial incontinence. The longest duration was 11 years, the shortest 3 months. The duration of incontinence in the remaining 5 cases was 5 years, 4 years, 3 years, 21 months, 8 months, and 3 months respectively. The incontinence followed suprapubic prostatectomy in 2 cases, perineal prostatectomy in 2, transurethral resection of the prostate in 2 and fracture of the pelvis with rupture of the urethra in 1. Four patients were cured by the operation, 2 improved, and there was 1 failure. The postoperative hospitalization period ranged from 16 to 56 days, averaging 32 days.

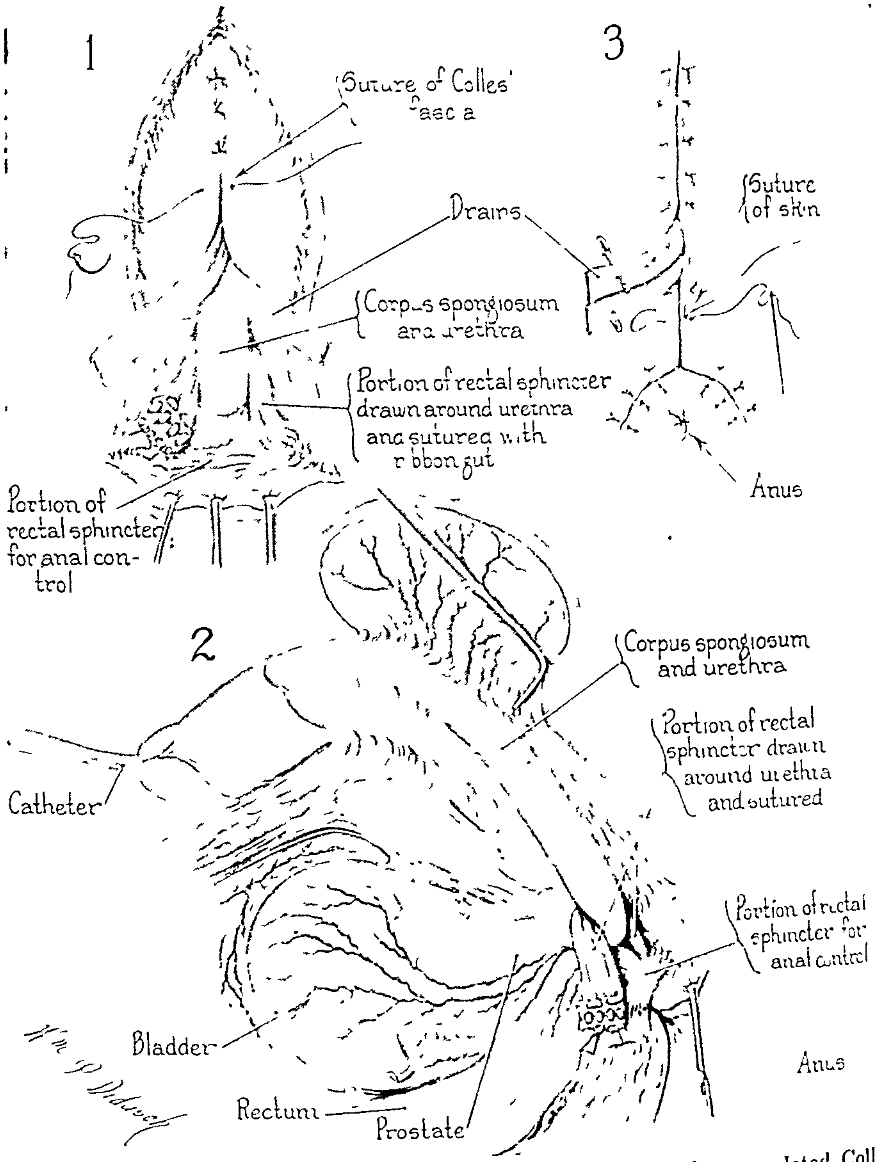
1
Suture of Colles' fascia
Drains
Corpus spongiosum and urethra
Portion of rectal sphincter drawn around urethra and sutured with ribbon gut
Portion of rectal sphincter for anal control
3
Suture of skin
Anus
2
Catheter
Corpus spongiosum and urethra
Portion of rectal sphincter drawn around urethra and sutured
Portion of rectal sphincter for anal control
Bladder
Rectum
Prostate
Anus

FIG. 6. *1*, Suture of portion of rectal sphincter drawn around urethra completed Colles' fascia sutured. *2*, Sagittal view showing suture of portion of sphincter drawn around urethra. Bulbous urethra drawn downward *3*, Suture of skin.

Brief protocols of the 7 cases follow:

Case 1. K. T. B., aged 67 years, was admitted to the hospital on June 19, 1949 for relief of complete urinary incontinence of 11 years' duration, following suprapubic prostatectomy. He had been wearing a rubber urinal and dribbled urine while prone and standing. On June 22, the Flaqué-Lowsley operation for incontinence was performed. The catheter was removed on the seventh day, at which time the patient had excellent control. Exercises were started 1 week later. He was discharged 22 days after operation. At the present time, he is able to hold 240 cc (about 2 hours' accumulation) of urine, with complete control.

Case 2. M. W., aged 58 years, was admitted on July 25, 1949 with urinary incontinence. Three months previously, he had had a transurethral resection and since then had been almost entirely incontinent, wearing a Cunningham clamp. Operation was done on July 27, and the Penrose drains and catheter were removed on the third day. The patient had difficulty voiding and 300 cc of urine was removed by catheterization. The following day he passed a small amount of urine and thereafter voided without difficulty. Exercises were started on the fourteenth day and he was discharged 2 days later. He now has excellent urinary control and is able to hold as much as 240 cc with ease.

TABLE 2. *Human cases*

CASE	AGE	INCONTINENCE			POSTOP. DAYS	RESULT	POSTOP. COMPLICATIONS
		Cause	Duration	Degree			
1	67	Suprapubic prostatectomy	11 yrs.	Total	22	Cured	None
2	58	Transurethral resection	3 mos.	Partial	16	Cured	None
3	43	Ruptured urethra and fractured pelvis	4 yrs.	Total	51	Cured	None
4	66	Suprapubic prostatectomy	8 mos.	Total	56	Failure	Urethroperineal fistula (finally healed)
5	66	Perineal prostatectomy	3 yrs.	Total	39	Imp.	Acute retention Perineal infection
6	59	Perineal prostatectomy	21 mos.	Partial	21	Cured	None
7	65	Transurethral resection	5 yrs.	Total	18	Greatly imp.	None

Case 3. E. B., a 43 year old diabetic, was admitted to the hospital on August 13, 1949 with total urinary incontinence. Four years previously, he had sustained a fracture of the pelvis with rupture of the urethra. This was repaired and a catheter left in for 9 days. A urethroperineal fistula healed in 7 days. Postoperatively he had a urethral stricture with partial incontinence. Eighteen months later, he had excision of the stricture with anastomosis of the cut ends, and following this had partial incontinence. Two years later, he had a Lowsley plastic

remaining 5 cases was 5 years, 4 years, 3 years, 21 months, 8 months, and 3 months respectively. The incontinence followed suprapubic prostatectomy in 2 cases, perineal prostatectomy in 2, transurethral resection of the prostate in 2 and fracture of the pelvis with rupture of the urethra in 1. Four patients were cured by the operation, 2 improved, and there was 1 failure. The postoperative hospitalization period ranged from 16 to 56 days, averaging 32 days.

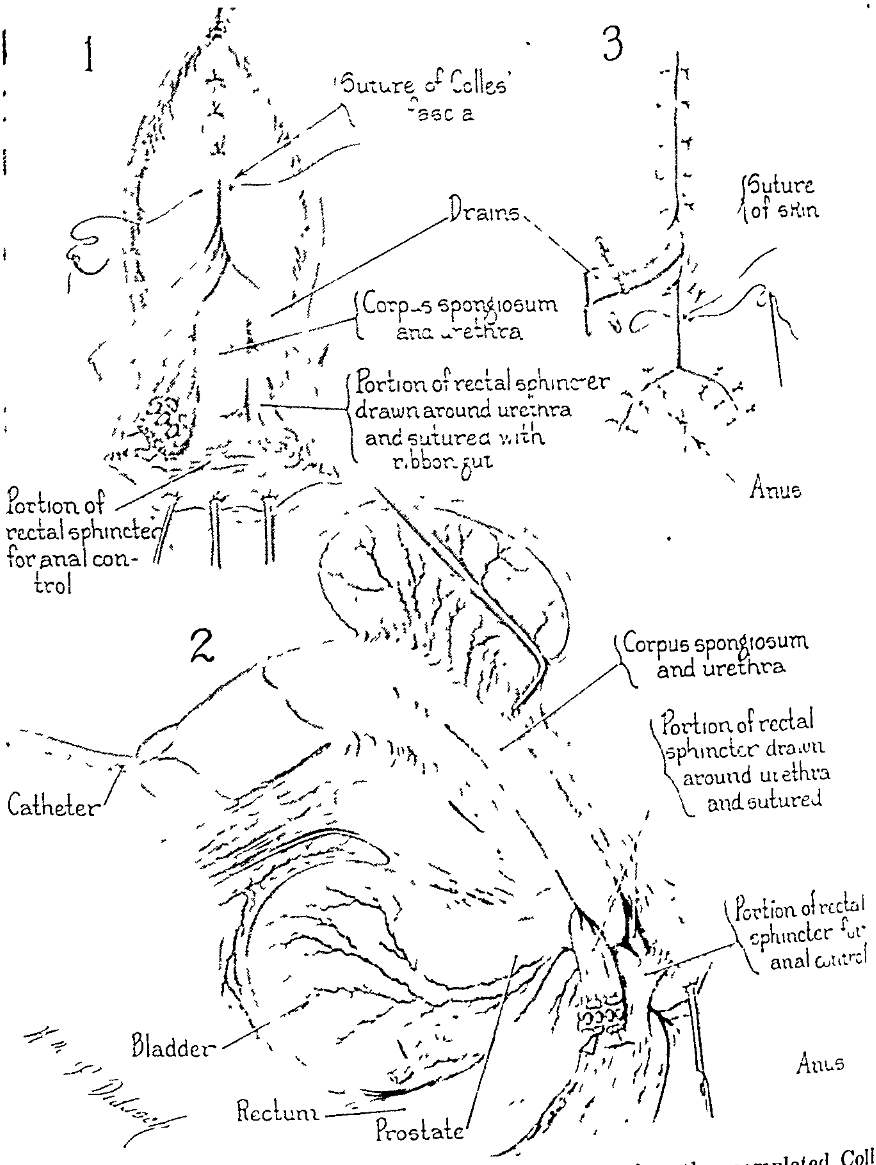
1
Suture of Colles' fascia
3
Drains
Suture of skin
Corpus spongiosum and urethra
Portion of rectal sphincter drawn around urethra and sutured with ribbon gut
Anus
Portion of rectal sphincter for anal control
2
Corpus spongiosum and urethra
Portion of rectal sphincter drawn around urethra and sutured
Catheter
Portion of rectal sphincter for anal control
Bladder
Anus
Rectum
Prostate

FIG 6. *1*, Suture of portion of rectal sphincter drawn around urethra completed Colles' fascia sutured *2*, Sagittal view showing suture of portion of sphincter drawn around urethra. Bulbous urethra drawn downward *3*, Suture of skin.

Brief protocols of the 7 cases follow:

Case 1. K. T. B., aged 67 years, was admitted to the hospital on June 19, 1949 for relief of complete urinary incontinence of 11 years' duration, following suprapubic prostatectomy. He had been wearing a rubber urinal and dribbled urine while prone and standing. On June 22, the Flaqué-Lowsley operation for incontinence was performed. The catheter was removed on the seventh day, at which time the patient had excellent control. Exercises were started 1 week later. He was discharged 22 days after operation. At the present time, he is able to hold 240 cc (about 2 hours' accumulation) of urine, with complete control.

Case 2. M. W., aged 58 years, was admitted on July 25, 1949 with urinary incontinence. Three months previously, he had had a transurethral resection and since then had been almost entirely incontinent, wearing a Cunningham clamp. Operation was done on July 27, and the Penrose drains and catheter were removed on the third day. The patient had difficulty voiding and 300 cc of urine was removed by catheterization. The following day he passed a small amount of urine and thereafter voided without difficulty. Exercises were started on the fourteenth day and he was discharged 2 days later. He now has excellent urinary control and is able to hold as much as 240 cc with ease.

TABLE 2. *Human cases*

CASE	AGE	INCONTINENCE			POSTOP. DAYS	RESULT	POSTOP. COMPLICATIONS
		Cause	Duration	Degree			
1	67	Suprapubic prostatectomy	11 yrs.	Total	22	Cured	None
2	58	Transurethral resection	3 mos.	Partial	16	Cured	None
3	43	Ruptured urethra and fractured pelvis	4 yrs.	Total	51	Cured	None
4	66	Suprapubic prostatectomy	8 mos.	Total	56	Failure	Urethroperineal fistula (finally healed)
5	66	Perineal prostatectomy	3 yrs.	Total	39	Imp.	Acute retention Perineal infection
6	59	Perineal prostatectomy	21 mos.	Partial	21	Cured	None
7	65	Transurethral resection	5 yrs.	Total	18	Greatly imp.	None

Case 3. E. B., a 43 year old diabetic, was admitted to the hospital on August 13, 1949 with total urinary incontinence. Four years previously, he had sustained a fracture of the pelvis with rupture of the urethra. This was repaired and a catheter left in for 9 days. A urethroperineal fistula healed in 7 days. Postoperatively he had a urethral stricture with partial incontinence. Eighteen months later, he had excision of the stricture with anastomosis of the cut ends, and following this had partial incontinence. Two years later, he had a Lowsley plastic

operation for relief of the impotence which followed the rupture of the urethra and 2 months after this a spinal fusion. This was followed by total incontinence. On October 17, 1949, the Flaqué-Lowsley operation was performed. The Penrose drain was removed on the third day and the catheter on the fifth day. He had good urinary control from the first, and to date has remained continent.

Case 4. H. S., 66 years old, was admitted on October 31, 1949 with total incontinence which followed a suprapubic prostatectomy 8 months earlier. Five months previously, he had had an unsuccessful perineal operation for relief of the incontinence. The Flaqué-Lowsley operation was done on November 2. During the operation, a small, partly closed fistulous tract connecting with the urethra was found and was excised. Postoperatively, upon removal of the catheter, the patient was unable to void, due to the angulation of his urethra. The catheter was reintroduced and in doing so it was necessary to reopen the perineal wound. This procedure was followed by extensive sloughing of his perineum, including a portion of the urethra. The incision finally healed, but during the process the graft from the anal sphincter evidently suffered complete necrosis, and he must be counted as a failure. He was discharged, unimproved, 56 days postoperatively.

Case 5. W. P., 66 years old, was admitted to the hospital on November 9, 1949 with total incontinence. Three years previously, he had had a perineal prostatectomy and thereafter had worn a Cunningham clamp which irritated his urethra so much that he changed to a pad. On November 10, the Flaqué-Lowsley operation was done. When the catheter was removed, on the sixth day, the patient was unable to void, and it was necessary to reinsert the catheter under anesthesia, with reopening of the perineal wound to guide it. Two days later he developed a urethroperineal fistula, which subsequently healed, and he was discharged 39 days postoperatively. At present, he has complete control while prone and can control his urine at other times if he voids frequently.

Case 6. M. R., 59 years old, was admitted on November 16, 1949 with partial incontinence which followed a perineal prostatectomy 21 months earlier. Exercises did not improve his condition, and 10 months before the present admission plication of his urethra was done through the perineum, which was followed by slight improvement. On November 17, 1949, partial incontinence still being present, the Flaqué-Lowsley operation was done. The catheter was removed on the tenth day. There was some urethroperineal leakage and it was reinserted and allowed to remain for another 8 days, at which time the wound was well healed. He was discharged 22 days postoperatively, still partially incontinent. Exercises at the office, for the next 3 months, resulted in progressive improvement until, at the present time, he has excellent control and holds 250 cc of urine, *with no* dribbling.

Case 7. R. B., 65 years old, was admitted to the hospital on April 3, 1950 because of complete urinary incontinence which followed a transurethral resection in 1945. One year ago, he had a perineal operation for incontinence, without improvement. The Flaqué-Lowsley operation was performed on April 4 1950. The catheter was removed on the seventh day, but there was some perineal leakage and it was reinserted 2 days later and allowed to remain for 9 days.

The patient was discharged on the eighteenth postoperative day, with the wound well healed and able to void small amounts of urine, but still leaking urine from the meatus in the standing position. At the present time, this patient does not leak at all in the recumbent position and can start and stop his stream successfully, but while ambulatory he does have partial incontinence.

SUMMARY AND CONCLUSIONS

Five of the 7 patients upon whom we have performed this operation had previous attempts at repair made by the perineal route, and these, of course, introduced a large amount of scar tissue and added to the difficulty of the procedure. However, the results obtained, even with this difficult type of case, have been so excellent in most instances that we are encouraged to try the operation upon anyone who seems to be in need of this particular type of procedure.

The one complete failure was upon a man (case 4) who was totally incontinent following suprapubic removal of his prostate gland and had had an unsuccessful attempt to relieve his incontinence by the perineal route. The scar tissue and the age and tissues of this individual militated against the operation and there was complete failure due to the sloughing out of part of the perineum, which then had to be restored by granulating in from the bottom.

In another (case 5), there was a mediocre result because the patient also had a massive infection of the perineum postoperatively, which interfered with proper healing. However, he now has complete control while in a prone position, and, while ambulatory, is without incontinence if he voids frequently.

The remaining 5 patients in the series have shown remarkably good results (4 cured, 1 greatly improved), which encourages us to recommend this operation to those patients who have not been cured of their incontinence by muscular exercises or other operative means.

DISCUSSION

Dr. Victor F. Marshall (New York, N. Y.): Urinary incontinence is still a major problem as witnessed by the numerous techniques devised for its correction. The incomplete understanding of the precise mechanisms of normal urinary control is most likely the fundamental reason that so many techniques are inadequate.

The procedures for the correction of urinary incontinence may be classified under six headings:

First, the urine may be transferred to another site, either behind an existing adequate sphincter or to a place where collection by artificial means is more suitable.

Second, a new sphincter may be constructed from foreign materials. Foley's artificial sphincter about the urethra is an example of this group as well as the too well known penis clamp. While the foreign material sphincters have much to offer in a deplorable situation, I hardly need mention their many disadvantages.

Third, a new sphincter may be constructed from tissues that are not normally sphincteric. The transplantation of the gracilis muscle about the urethra is a well known example. If this gracilis transplantation were highly successful, it seems unusual that the reporting of a large series of successful cases has not made it a popular procedure. As far as I can see, a totally new physiologic sphincter which is adequate to control urine and which is under voluntary nervous control, has been constructed only by the Almighty Himself.

Fourth, the existing specific sphincter may be repaired. Reapproximations and plications of the anal sphincter, for instance, are often successful but surgical reapproximation of the external urethral sphincter following sharp division is a rare operation.

Fifth, the mechanical advantage of the existing specific sphincter may be improved. This is perhaps best illustrated by the elevation and fixation of the existing mechanism so commonly accomplished by the standard gynecological operations for stress incontinence.

Sixth, and finally, another existing sphincter may be substituted in whole or in part for the specifically urinary sphincter which is inadequate. This would seem to be a particularly promising field. Dr. Flaqué's operation falls in this group. As such I believe it has a good prospect for success. I have witnessed the operation and certainly it does not appear technically difficult. The procedure is new and I feel sure that Dr. Flaqué will not only improve it but investigate its limits of application.

In brief, the principle upon which the operation is based is theoretically sound. The results reported are impressively good and I believe the procedure could develop into one of the best methods for the control of urinary incontinence in the male.

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FEMALE PSEUDOHERMAPHRODITISM WITH SUPPLEMENTARY PHALLIC URETHRA: REPORT OF TWO CASES

FREDERICK S. HOWARD AND FRANK HINMAN, JR.

From the Department of Surgery-Urology, University of California Medical School, San Francisco, Calif.

Congenital urethrovaginal communications are extremely rare and the presence of a urethra throughout the length of the clitoris is almost unheard of. This paper concerns 2 girls with both of these anomalies, treated for them at the University of California Hospital. Most female pseudohermaphrodites represent examples of the congenital adrenogenital syndrome and are primarily an endocrinological and social problem. Although the adrenal disturbance causes progressive endocrine and metabolic changes in the entire body, ordinarily these individuals have no major uropathy leading to untoward urinary symptoms or renal damage. In our cases, however although the masculinization of the external genitalia was sufficient to cause doubt as to sex, the social problems arising from this were far overshadowed by associated secondary changes in the urinary tract. Their diagnosis and treatment present an interesting urologic problem.

REPORT OF CASES

Case 1. S. E. was seen at the age of 1 day because of a tumor in the lower abdomen reaching just above the umbilicus. There was no family history of congenital anomalies except a maternal cousin who had a bipartite vagina. Examination of the abdomen revealed a mass which felt like a distended bladder rising to above the umbilicus. The clitoris was markedly enlarged, had a tiny meatus on its glans and was hooded by a dorsal prepuce. It was only moderately incurvated. The labia majora were normal in appearance without palpable organs or masses within them. The vaginal orifice was small and transverse, and lay in a position corresponding to the posterior portion of the normal introitus. No signs of a hymen were present. The area between the vaginal introitus and the base of the clitoris was occupied by a thick curtain of tissue made up of fused labia minora. The anus was normal. Urine could be seen escaping at intervals in small spurts both from the urethral meatus on the glans of the clitoris and from the vaginal orifice. Catheterization of the vaginal orifice yielded 200 cc urine without the size of the suprapubic mass decreasing particularly. Shortly after the catheterization of the vagina, the child began to put out large amounts of urine through the vaginal orifice and the hypogastric mass disappeared in 24 hours.

Excretory urograms were normal except for some lateral displacement of the lower ureters. Examination of the vagina with the cystoscope was not very satisfactory, but a urethral meatus was found on the anterior wall just proximal to the fused labia. It could not be catheterized. The phallic urethra was too small to admit a filiform or probe. X-rays taken after filling the vagina with radio-opaque salt showed 2 large saccular cavities, one just to each side of the midline occupying the pelvis. These were erroneously taken to be wolffian duct cysts.

Since the child was doing well medically, it was decided to keep her under observation and to correct her anomalies at the age of 3 or 4 years.

She re-entered the hospital on October 4, 1946 at the age of 4 years, having been perfectly well in the interval. The clitoris was still large (figs. 1 and 2). Cystoscopy showed that the vagina was tremendously enlarged, having a capacity of 300 cc. It was bipartite and a cervix could be seen on each side of the partition high up in the vault. The configuration of the vagina was demonstrated by x-ray (fig 3). The cystoscope could be passed through the urethral meatus into the bladder, disclosing a mild cystitis but no other abnormality. The ureters were catheterized without difficulty. Examination of the bladder urine showed pus and bacteria, but the kidney urines were negative microscopically and culturally. Pyelograms showed that the lower ureters were displaced laterally by the large vagina. There was slight dilatation of both ureters in their lumbar portions but no hydronephrosis. It was not possible to determine the connection between the phallic urethra and the remainder of the urinary tract either by cystoscopy or by probing the phallic urethra since it was too small to permit instrumentation. By leaving a catheter inlying in the vagina it was found that the child was able to void at intervals and to remain dry between voidings. Her incontinence had been caused simply by pooling of urine in the tremendously dilated vagina.

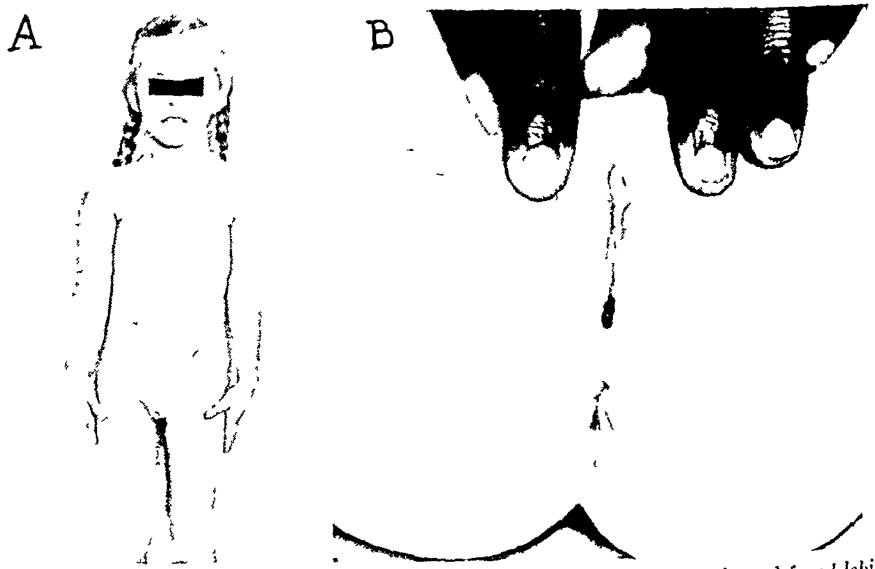

FIG. 1. Case 1. *A*, photograph of patient. *B*, showing enlarged clitoris and fused labia minora.

Her growth and development were in the upper limits of normal for her age. The bone age was not abnormally increased. Urinary gonadotrophic hormone and 17-ketosteroid excretion were normal. There was nothing to suggest that the genital anomalies were caused by adrenal hyperfunction.

On October 18, 1946, the abdomen was opened through a lower midline incision. A complete reduplication of the uterus with a normal tube and ovary on each side was found. The vagina projected far out into the abdominal cavity behind the bladder and was for the most part covered by peritoneum (fig. 4). Manual exploration of the kidneys and adrenals gave negative findings. Biopsy and tissue section of the ovaries showed them to be normal (fig. 5). A segmental resection of the major portion of the tremendous vagina was performed including

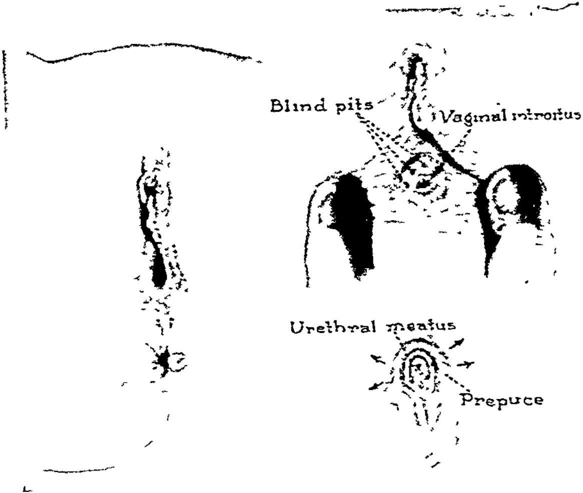

FIG. 2. Case 1. Drawing of external genitalia

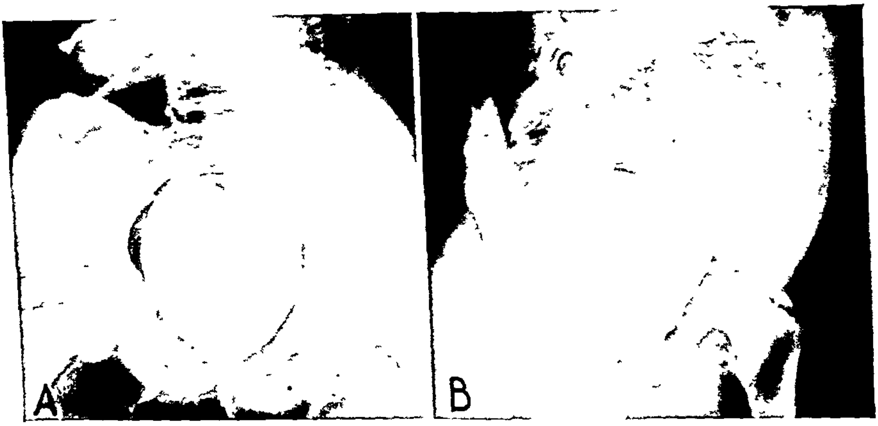

FIG. 3. Case 1. Bladder is filled with air and large bipartite vagina is outlined with opaque medium. Anteroposterior and lateral views.

the septum (fig. 6). A catheter was left through the urethra into the bladder to protect the vaginal suture line from urine.

The patient had an uneventful course following this procedure. On October 31, 1946 the fused labia minora were incised and a central wedge resected to open the vaginal orifice. Because of the experience in case 2, the vaginal mucosa was removed between the urethral meatus and the exterior along the anterior and lateral aspects of the vagina and this raw area was covered by two large skin flaps taken from the base of the clitoris. These were sutured to the sides of the vagina and also anteriorly at the urethral meatus to provide free egress of

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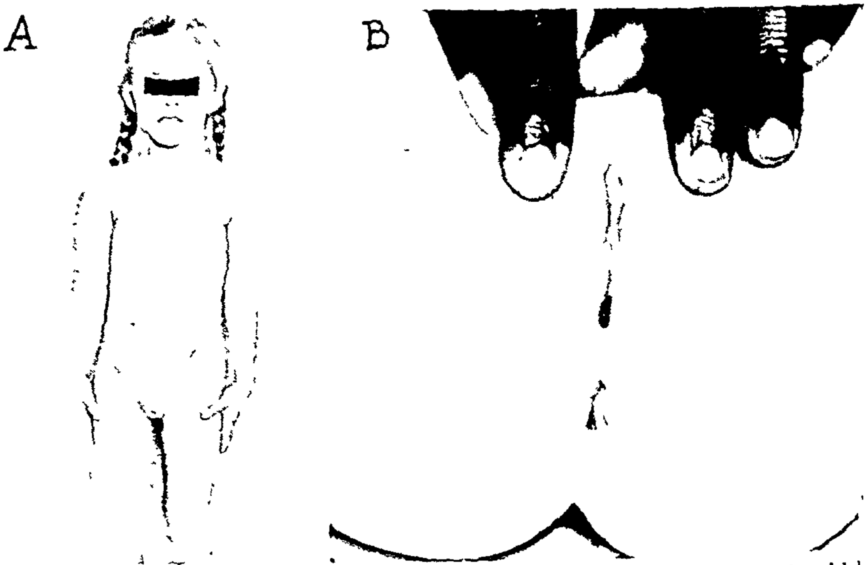

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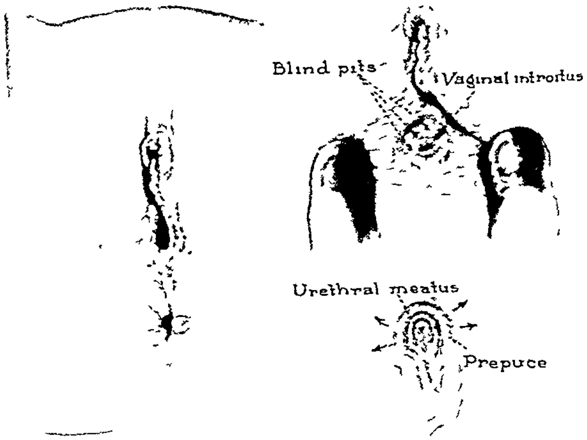
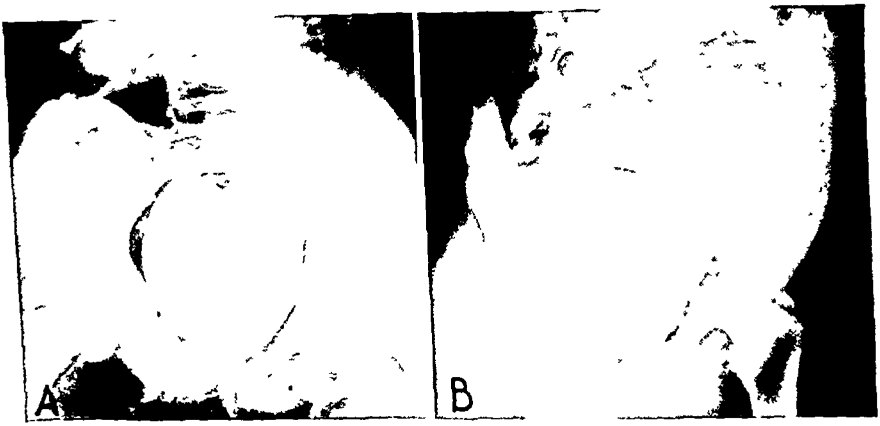


FIG. 2. Case 1. Drawing of external genitalia



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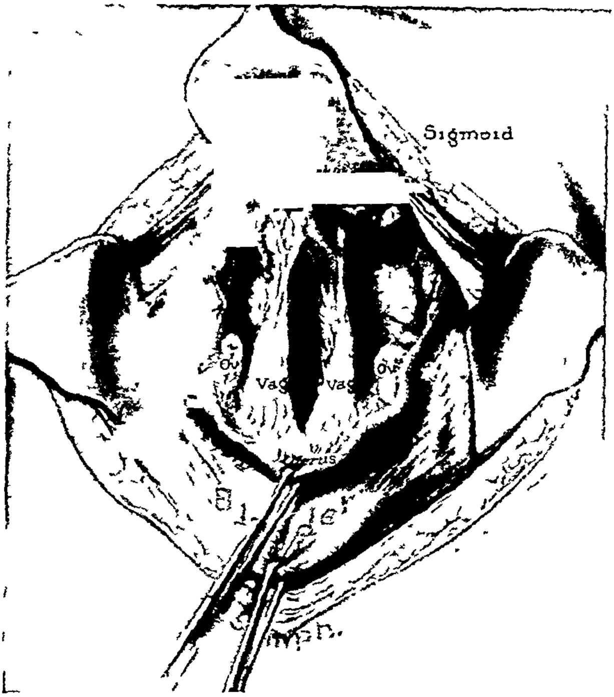

Fig. 4. Case 1. Drawing of large bipartite vagina, at operation

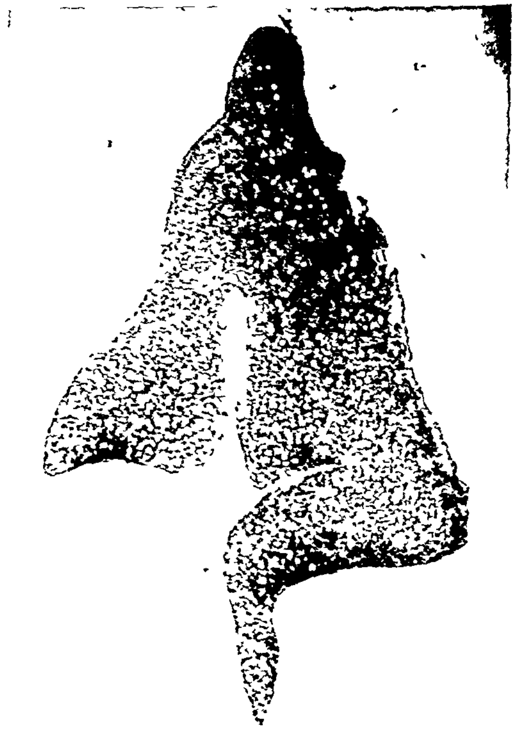

Fig. 5 Case 1. Section of ovary Normal prepuberal ovarian tissue

urine and also to avoid agglutination of the labia minora. The clitoris was not removed since its removal at the same time might have compromised the blood supply to the skin flaps. The urinary stream was diverted by suprapubic cystostomy. Following per primam healing of the vaginal area, the cystostomy tube was removed, the patient voided and the suprapubic sinus closed promptly.

She returned 6 months later for amputation of the clitoris. By this time she had perfect urinary control with no difficulty in voiding and no enuresis. The urine was negative microscopically and culturally. There was no residual urine. The urethra still opened within the vaginal orifice but the child's voiding was functionally normal. The vagina was still large but had not increased in size since it had been resected. The clitoris was removed. Sections showed corpora cavernosa, a small urethra, but no corpus spongiosum (fig. 7).

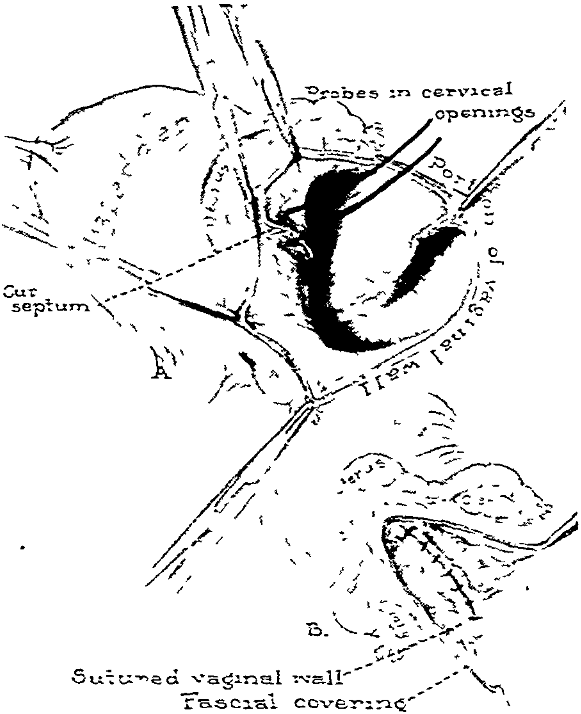

FIG. 6. Segmental resection of redundant vagina and vaginal septum

The child has been seen at intervals since and the result of the surgical treatment is good both from the cosmetic and the physiologic standpoints.

Case 2. R. G. entered the hospital on July 15, 1943, at the age of 3 years with the complaint of complete urinary retention. The child was born at term by a normal delivery. There was no family history of congenital anomaly. She has 2 normal older sisters. Another sister had died of meningitis at the age of 2 years. At birth, the child was pronounced a boy with undescended testicles. It was noted that a vaginal orifice was present but the phallus was extremely well developed and its glans contained a urethral meatus. She had been a feeding problem in infancy and at the age of 3 months pus was found in the urine. She had always dribbled constantly through the vaginal orifice but on effort could expel a stream both from the vagina and from the clitoris. For 18 hours prior to entry, she had passed no urine at all and had developed a large lower abdominal tumor.

On examination, the child appeared pale and underweight. The bladder was distended to just above the umbilicus. The external genitalia consisted of a phallus $1\frac{1}{2}$ cm. long with moderate ventral curvature. There was a circumferential prepuce which on retraction revealed the glans with a pinpoint urinary meatus from which urine was voided in small amounts. The labia majora appeared normal and empty. The labia minora were fused anteriorly with a transverse vaginal orifice far posteriorly in the vulva. Efforts to catheterize the bladder either through the vagina or the phallus were unsuccessful. A few ounces of urine were obtained from the vagina but the bladder could not be emptied. Suprapubic cystostomy was performed.

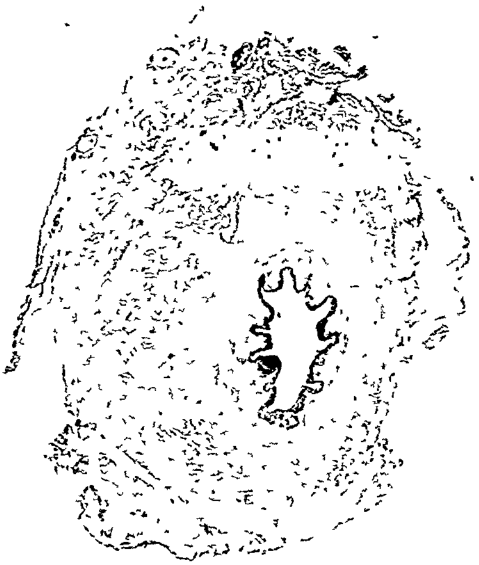

FIG. 7. Case 1. Cross section of phallic urethra. Note corpora cavernosa

The child withstood the procedure well. Several days after cystostomy she occasionally would void a little urine through the clitoris but nearly all the urine escaped incontinently through the vagina. Phenolsulfonphthalein excretion was normal, but excretory urography showed an atrophic left kidney, while the right kidney was hypertrophied. There was no hydronephrosis or hydro-ureter. A cystoscope passed into the vagina showed a vaginal urethral orifice 1 cm from the fused labia on the anterior wall of the vagina. This orifice was tight to a 16 F instrument but was easily dilated to 24 F. The vagina was much broader than normal and measured 8 cm. in length. A cervix could be seen in the vault. Passage of the cystoscope into the bladder showed it to be large and flaccid with a minor degree of coarse trabeculation. The bladder neck was normal and the urethra was normal except for the meatus. The communication between the phallic urethra and the remainder of the urinary tract could not be found. The right ureteral orifice was normal. The left ureteral orifice lay in a deep cellule and could not be catheterized.

Following urethral dilatation the child was able to void. The suprapubic tube was removed, the sinus closed, and she was discharged from the hospital.

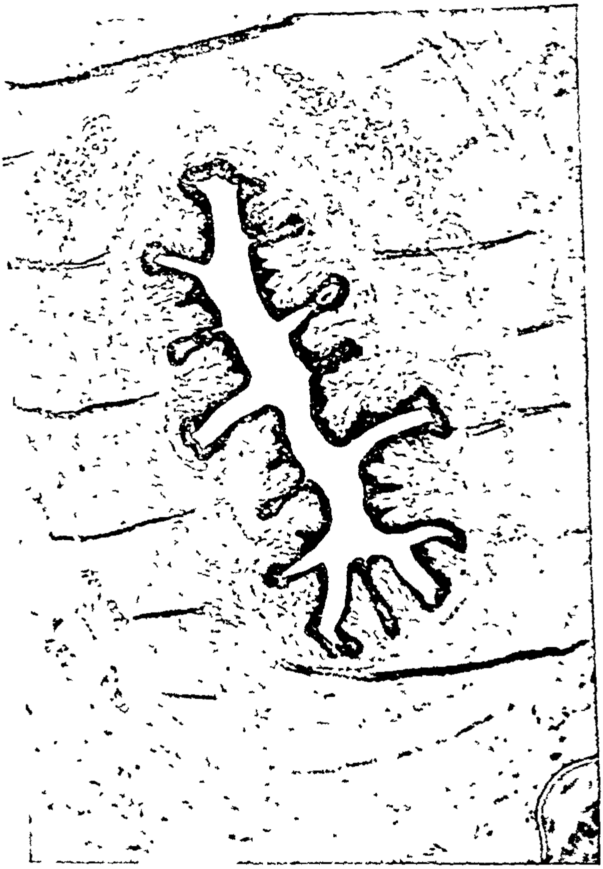

FIG. 8. Case 2 Cross section of phallic urethra Note corpora cavernosa

She re-entered the hospital on September 23, 1943, for determination of sex. At this time she was able to void approximately every hour during the day with considerable dribbling between voidings. She did not void at all at night and awoke each morning with a full bladder and had some difficulty in emptying it.

On October 8, 1943, the abdomen was explored. The internal genitalia were normal. Biopsy of the ovaries gave normal findings. The right kidney was enlarged and the left kidney very small. No adrenal enlargement was palpable. The clitoris was amputated. Sections of the clitoris showed the same findings as in case 1 (fig. 8). Following this procedure, the child's designation was changed from male to female, pleasing both the child and her parents.

Voiding improved for a time, but after a few months she began to have repeated episodes of retention followed by dribbling. On April 25, 1944, the vaginal introitus was incised longitudinally. Although digital dilatation of the introitus was practiced, the labial synechiae recurred. The operation was repeated several months later using vulval skin flaps through the introitus down to the urethral meatus with success.

This child has developed normally as a girl. Bone age and 17-ketosteroid excretion have been normal. She has negative urine, no residual urine, and normal kidney function by the phenosulfonphthalein test. She has no urinary symptoms except for occasional episodes of acute retention occurring in the mornings when the bladder has become too full, for which catheterization has been necessary several times. These episodes are decreasing in frequency and between them, micturition is normal. No urethral or vesical neck obstruction can be demonstrated. Because they only occur after a long sleep during which a large amount of urine has collected, some consideration has been given to the possibility that poor support to the base of the bladder allows obstructive kinking at the vesical neck to occur with over-distention.

DISCUSSION

These children belong to the "female hypospadias" or "vaginal urethra" group of congenital anomalies. Textbooks confusingly tend to place all congenital urethrovaginal communications under the single heading of "female hypospadias." Actually, Blum in 1904 clearly divided them into 3 entirely different groups consisting of 1) a deficiency of the posterior wall of the urethra and the anterior wall of the vagina producing a longitudinal communication between the 2 organs, 2) persistence of the urogenital sinus, the vagina entering the urethra, and 3) vaginal urethra where the urethra terminates within the vagina proximal to the hymen.

Little has been added to Blum's work except to separate etiologically his second and by far the largest group from the other two. Communication of the vagina with the urethra to form a common urogenital passage coursing along the ventral surface of the phallus for a varying extent is a part of the congenital adrenogenital syndrome and represents a hormonal masculinization of the fetal female urogenital sinus by hyperactivity of the adrenal cortex. There is no particular predisposition to disease of the urinary tract in these cases and the clinical problem is principally endocrinologic and sociologic rather than urologic.

Cases of Blum's first group of vaginal urethras, in which there is a longitudinal cleft in the dorsal wall of the urethra frequently involving the urinary sphincters are extremely rare. In this condition, the anterior and lateral portions of the urethra extend out to the position of the normal meatus. The posterior wall of the urethra, the anterior wall of the vagina, and the urethrovaginal septum are deficient. This is not associated with masculinization and appears to be simply the result of a local developmental defect in the urethrovaginal septum. When the defect extends through the sphincters, the individual is incontinent.

The third and apparently most rare of Blum's groups is the one in which our two patients should be classified. The principal characteristic of this group is a well formed but short urethra entering the vagina proximal to the hymen. There is also a frequent association of fusion of the anterior portion of the labia minora and hypertrophy of the clitoris. Despite hypertrophy of the clitoris, other evidences of masculinization are lacking. Double vagina is frequent. The vagina is often greatly enlarged probably because of hydraulic distention in fetal life. Lower urinary tract obstruction is frequently seen, although the cause for it is not clear. Autopsy after death from renal failure provides the majority of case records available in the literature. The contrast between this condition and persistence of the urogenital sinus is shown in figure 9.

The literature reveals scattered case reports and small series of vaginal urethra with or without hypertrophy of the clitoris or vaginal anomalies (Blum, Zuppinger, Kermauner). However, we were able to find the report of only 1 case with a clitoridean urethra, a case identical with ours. This was published by Grubenmann in 1912 and presented the autopsy findings in a 3 year old female pseudohermaphrodite dying of chronic retention and urosepsis. Although in Blum's case there was a urethral groove along the ventral surface of the clitoris, the case of Grubenmann had both a vaginal urethra and a complete supplementary phallic urethra traversing the length of the hypertrophied clitoris. The ovaries and adrenals were normal. The uterus was bicornuate and the vagina large and bipartite. The labia minora were agglutinated anteriorly in front of the vaginal urethral orifice. The phallic urethra extended from the glans clitoridis to an internal orifice in a small bladder diverticulum just anterior to the vesical neck. The phallic portion of the urethra lacked a corpus spongiosum, and there was no evidence of prostate or seminal vesicles. Rudimentary urethral musculature was present. No clear cut cause of the lower tract obstruction responsible for the child's death could be found, but Grubenmann thought that it might have been caused by filling of the diverticulum anterior to the neck of the bladder so that it pressed upon the internal orifice of the major urethra.

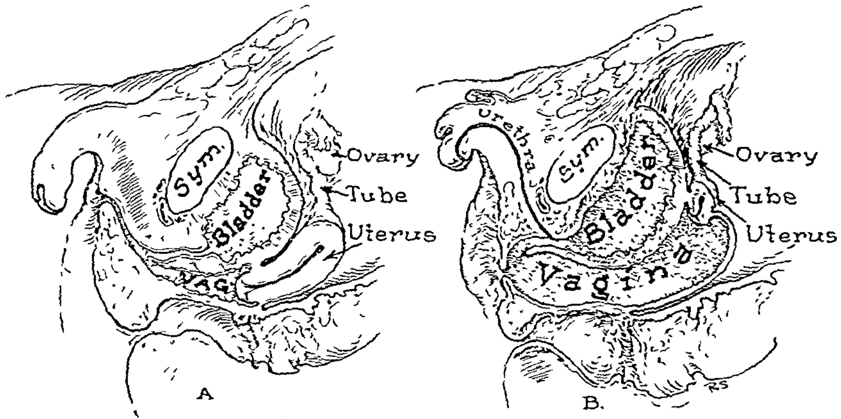

FIG. 9. *A*, persistent urogenital sinus (a more common anomaly). *B*, vaginal urethra (a rare anomaly) with accessory phallic urethra.

The mechanism of altered development causing this type of vaginal urethra cannot be determined with exactness. Both from the literature and from the clinical study of our patients, it is probable that a local developmental disturbance rather than a generalized intersexual type of development is responsible. This is particularly supported by the entirely different anatomical configuration observed in the congenital adrenogenital syndrome and in the artificially produced persistence of the urogenital sinus in the female young of experimental animals administered androgen during pregnancy (Greene, Moore).

The developmental fault affects primarily the pars phallica of the urogenital sinus and the caudal ends of the müllerian ducts thus dating it to an early stage of development. Both Blum and Grubenmann felt that the primary fault was a slowing of the downward growth and fusion processes of the müllerian ducts. According to this hypothesis delayed or slow union of the müllerian ducts with the urogenital sinus removes an inhibitive influence from the pars phallica allowing it to go through independent contrasexual development. This explains, as a purely local phenomenon, the occurrence of hypertrophy of the clitoris and, in these cases, an accessory phallic urethra without other masculinizing changes.

The potentiality of the urogenital sinus to follow either a masculine or a feminine line of development despite the gonadal sex of the embryo is well established clinically and experimentally (Greene, Moore). The concept of a co-ordinated development of the embryo subject to local stimulation or inhibition of its various parts by adjacent cells is not so well established. However, the experimental production of anomalies in fish by Stockard lends much support to this theory. The development of fish ova can be retarded by lowering the temperature or the oxygen content of their environment. The developmental rates of an embryo as a whole and of its component parts are not uniform and each part has its periods of rapid progress and relative quiescence. Stockard showed that temporary artificial slowing of development had little or no effect upon structures which at the time of its application were developing slowly but a profound effect upon those parts of the embryo undergoing rapid growth and differentiation. In the 25 mm. embryo, the müllerian ducts have reached the urogenital sinus (fig. 10). At this time the pars phallica is in an indifferent stage from which in both sexes definitive differentiation of the external genitalia begins. In the succeeding weeks, in the male there is a rapid development of the wolffian duct structures and of the pars phallica with recession of the müllerian ducts. In the female the same stages are dominated by the downward growth of the müllerian ducts and the ingrowth of urogenital sinus epithelium into them at Müller's hillock. If it is assumed that this growth process dominates the region at this time, it follows that differentiation of the pars phallica is impeded by the marked activity at Müller's hillock. Should the process of müllerian duct growth and union with the urogenital sinus be slightly delayed or impaired in intensity, and then later accelerated, the anomalies to be expected are 1) a slightly cranial location of Müller's hillock manifested by a vaginal urethral meatus and 2) a certain degree of inhibition of the development of the pars phallica, manifested by agglutination of the labia minora and hypertrophy of the clitoris with or without development of an accessory rudimentary masculine urethra.

The hypothesis of defective müllerian duct development as a primary cause is supported by the associated fusion defects of bipartite vagina and reduplication of the uterus. The fact that congenital absence of the vagina is not associated with clitoridean and urethral anomalies does not detract from the explanation, since the evidence indicates that this condition is not based upon a delay of fusion with the urogenital sinus but rather upon a failure of recanalization of the ducts after union or a generalized lack of definitive development of the ducts themselves changes taking place a a later stage of development than the formation of a phallic urethra. Finally, a theory might be proposed that the primary fault in vaginal urethra lies in an early ascendancy of the development of the pars phallica with secondary interference of müllerian duct development. Were this the right explanation one would expect all individuals with a vaginal urethra of this type to have hypertrophy of the clitoris and masculine urethral development, which is not true. Also if the primary point of developmental aberration were in the pars phallica, one would expect the entire urethra to be masculine in type with the vagina entering it rather than to have the phallic urethra absent or rudimentary, as is the case. We therefore agree with the hypothesis of the older workers that the condition arises primarily from a defect in müllerian duct and urogenital sinus fusion either in time or intensity with a secondary local masculinization of the pars phallica due to lack of inhibition of its development.

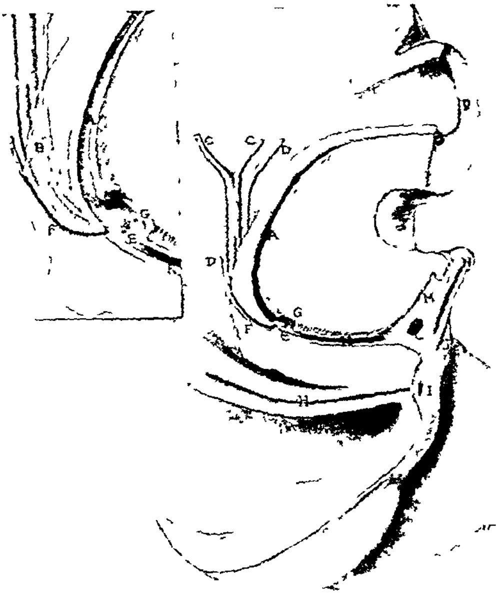

Fig. 10. Schematic drawing of 25 mm human embryo. (Partially adapted from Keibel and Mall and from Spaulding.) *A*, vesico-urethral anlage. *B*, beginning separation of mullerian duct. *CC*, mullerian ducts. *DD*, wolffian ducts. *E*, mullerian tubercle. *F*, right wolffian duct. *G*, opening of left wolffian duct. *H*, hind gut. *I*, anus. *J*, labio-scrotal swellings. *K*, pars pelvina sinus urogenitalis. *L*, pars phallica sinus urogenitalis. *M*, urogenital membrane. *N*, phallic tubercle. *O*, urachus. *P*, umbilical cord.

CLINICAL ASPECTS

The clinical problems presented by our 2 cases and by the similar ones in the literature have been both urologic, connected with incontinence and retention, and social, connected with the diagnosis of sex. In contrast with all other general types of pseudohermaphroditism, the diagnosis and treatment of the urinary tract disturbance is of the greatest magnitude far overshadowing the question of sex determination.

The incontinence in these cases is a false incontinence caused by the collection of voided bladder urine in the large vagina. They should not be confused with the unrelated cases of deficiency of the urethrovaginal septum loosely also termed "female hypospadias" in which the incontinence is true. The capacity of the vagina is so great as to permit the passive accumulation of several ounces of urine producing a constant dribbling from the introitus. Secondary infection of the pooled vaginal urine is inevitable and is followed by early spread to the urethra and bladder and later to the upper tract. Incontinence is readily relieved by giving the vaginally situated urethral orifice free egress to the outside.

The cause of retention of urine in these individuals is not clear but appears to be directly related to the accumulation of urine in the vagina. Zuppinger reported an obvious stricture of the urethra in 1 case, a woman of 90 years, and attributed chronic retention in another case to the same cause although it persisted during months of repeated urethral dilatation. Grubenmann attributed the urinary obstruction in her case to a diverticulum of the bladder near the internal urethral orifice. Blum felt that angulation of the vesical neck on overdistention of the bladder was the cause of retention. In 1 of our 2 cases, the distended bladder present 24 hours after birth emptied itself soon after catheterization of the vagina. In that patient, there was little evidence of urinary tract damage and no recurrence of retention. However, her vagina was emptied daily by catheter and irrigated with an antiseptic solution until after surgical correction of the anomaly. In the other patient, seen at the age of 3 years, retention was recurrent until free egress of urine from the vaginal orifice was secured by surgery. We are not sure of the cause of retention but feel that it is probably primarily due to inflammatory changes in the urethra secondary to pooling of urine in the vagina plus the mechanical disadvantage of constantly voiding into the vaginal pool. In any case, a surgical procedure to keep the vaginal orifice open and to allow a free flow of the voided urine to the outside is indicated.

The question of sexuality is naturally of importance since the external genitalia present characteristics of those of both sexes. Both because of the gonadal, genetic, and endocrine femaleness of these individuals and because of the aforementioned urinary tract disturbance it is most important that they not be regarded as males with undescended testes and urinary fistulas. Observation of these children as such leads to progressive urinary damage and in the past has been a common cause of death. Differentiation from the female pseudohermaphroditism of the congenital adrenogenital syndrome is important since the latter condition is a generalized and progressive adrenal cortical masculinization without any satisfactory treatment to arrest or reverse this process. Whether adrenogenital pseudohermaphrodites should be raised as girls or boys, despite the presence of ovaries, is a matter of dispute since the general somatic attributes when full development is reached is more masculine than feminine (Wilkins). Decision as to which sex to convert the external genitalia in these cases must be based upon careful consideration of psychic and endocrine factors. Amputation of the hypertrophied clitoris at an early age is not recommended unless the environmental factors are hopelessly against toleration of a pseudohermaphrodite in the family until psychic sex asserts itself. In vaginal urethra with hypertrophy of the clitoris and accessory phallic urethra, there is no evidence of a persistent masculinizing influence and clitoridectomy is indicated. Conversion to the female is relatively simple, while conversion to the male would involve extensive plastic surgery because of the deep location of the vaginal urethral meatus and the hopelessly inadequate caliber of the phallic urethra. The differential diagnosis is not difficult, since this is the only known intersexual condition where the urethra enters the vagina. In the adrenogenital syndrome and in male pseudohermaphroditism with hypospadias and vaginal development, the vagina enters the urethra or their orifices occupy the normal female relationship (Howard). However, until further accumulation of cases brings about full recognition of this clinical syndrome, studies for determination of adrenal cortical hyperactivity by bone age and urinary 17-ketosteroid excretion and laparotomy for examination of the gonads is recommended before plastic procedures are done on the external genitalia.

SUMMARY AND CONCLUSIONS

The pathological anatomy and surgical treatment of 2 cases of a rare syndrome of female pseudohermaphroditism consisting of vaginal urethra, hypertrophy of the clitoris, and complete accessory phallic urethra, are described.

These anomalies are believed to result from a purely local developmental error consisting of retardation of union between the müllerian ducts and the urogenital sinus either in time or intensity with secondary uninhibited development of an accessory urethra by the pars phallica.

Distinction is made between this condition and other congenital urethrovaginal communications.

Emphasis is laid upon the recognition of this syndrome which, in contrast to all other intersexual conditions, carries a grave risk of urinary tract complications.

REFERENCES

Blum, V.: Die Hypospadie der weiblichen Harnröhre. Monatsbericht f. Urol., 9: 522–543, 1904.

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Greene, R. R.: Embryology of sexual structure and hermaphroditism. J. Clin. Endocrinol., **4**: 335–348, 1944.

Grubenmann, I.: Eine Sagittale Verdoppelung der weiblichen Harnröhre. Frankfurt. Ztschr. f. Path., **10**: 101–128, 1912.

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Keibel, F. and Mall, F. P.: Manual of Human Embryology. Philadelphia: J. B. Lippincott Co., 1912.

KERMAUNER, F.: Fehlbildungen der weiblichen Geschlechtsorgane, des Harnapparates und der Kloake. Fragliches Geschlecht. *In*: Halban, J. & Seitz, L.: Biologie und Pathologie des Weibes, band 3, pp. 280-620. Berlin: Urban & Schwarzenberg, 1924.

MOORE, C. R.: Sex endocrines in development and prepuberal life. J. Clin. Endocrinol., **4**: 135-141, 1944.

SPAULDING, M. H.: The development of the external genitalia in the human embryo. Contrib. Embryol. (Carnegie Inst.), Wash., **13**: 69-88, 1921.

STOCKARD, C. R.: Developmental rate and structural expression: an experimental study of twins, "double monsters" and single deformities. Am. J. Anat., **28**: 115-277, 1921.

WILKINS, L.: Abnormalities and Variations of Sexual Development During Childhood and Adolescence. New York and London: Advances in Pediatrics, Interscience Publishers, **3**: 159-218, 1948.

ZUPPINGER, C.: Zur Kenntniss der Urethra vaginalis und deren Folgenzustände. Arch. f. Kinderheilk., **39**: 303-316, 1904.

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PARAFFINOMA OF THE PENIS: CASE REPORT

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Paraffinomas are tumors resulting from the presence of paraffin or mineral oil in the tissues. They occur chiefly as the result of injudicious or unwittingly misguided therapeutic procedures. Mineral oil compounds are still introduced into the body for many purposes. Paraffinomas ensue sufficiently often to make certain the conclusion that mineral oils are not totally innocuous.

Paraffin tumors were first recognized 40 years ago when the vogue for paraffin prostheses reached its height. This practice was originated in 1899 by Gersuny, who injected paraffin with a melting point of 40 C into the scrotum of a young man to replace testicles removed because of tuberculosis. The effect was successful and permanent despite a subsequent elevation of temperature to 40 C. Gersuny thereafter successfully injected paraffin into the vesical mucous membrane to remedy incontinence of urine. His procedure was at once widely adopted, at first for the correction of sphincter incontinence and hernias, later for the correction of cleft palates, atrophic rhinitis, permanent separation of divided nerves and for restoration of facial deformities. In 1904, Eckstein reported the successful use of the method in over 2000 cases of deformities of the palate and face.

Heidingsfeld in 1906 published the first description of the tumors which began to appear as a result of these injections. Benedek applied the term paraffinoma to them in 1913. Since then, many papers have been published on the subject. Paraffinomas of the face, nose, lung, breast, peritoneum, hand, knee, and ankle are recorded. All are characterized by the same pathologic picture: a connective tissue new growth resembling granulomas, and containing a series of oval or round cavities like Swiss cheese filled with oily matter. Macrophages and giant cells are present, but caseation is rare. The tumors usually develop six to fifteen months after the introduction of the paraffin. Masses of varying size appear in the subcutaneous tissue attached to the epidermis. They are bluish red, brownish red, or pale. The vessels of the overlying skin are distended and fill slowly after pressure. They cause no discomfort aside from the pressure and edema. Disfiguration is marked. Tumors do not always develop following injections of paraffin. Differences in reaction may be due to varying degrees of purity of the oil, but apparently the determining factor is sensitivity of the patient's tissues.

Paraffin granulomas continue to be found in many unusual locations due to the injudicious use of mineral oil compounds. Considerable clinical interest was aroused a decade ago by the recognition of paraffinomas of the lung ensuing from prolonged use of nose drops with an oily base. Such nose drops are now condemned for this reason. More recently it has been shown that significant amounts of mineral oil taken by mouth as a laxative reach the lung and that this accounts for nearly half of the adult cases of oil respiration pneumonia.

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Atlantic City, N. J., March 31, 1949.

Paraffinoma formation in the mesenteric lymph nodes has been recognized resulting from the regular use of mineral oil as a laxative, especially in cases of diverticulosis of the large bowel. Numerous enterprising surgeons have made the mistake of attempting to prevent adhesions by introducing mineral oil into the peritoneum before closing the abdomen. The results have always been disastrous. Extensive paraffinoma formation ensues, with intestinal obstruction an inevitable outcome.

The diesel engine and the high pressure grease gun have contributed to the occurrence of paraffinomas of the hand. Diesel engine mechanics who test carburetor jets with their fingers receive small quantities of diesel oil subcutaneously. This may result in gangrene of the finger tips, or later paraffinoma formation of the palmar spaces. A similar sequence of events follows the injection of grease from high pressure grease guns. The pathology and treatment of this type of oleoma have been fully reported by Mason and Queen.

Hundreds of cases are recorded in the foreign literature in which paraffinomas resulted from the efforts of malingerers to alter their appearance to avoid military conscription. Malignant degeneration of a paraffinoma rarely occurs. Only two such instances are on record.

Paraffinomas of the penis have been previously reported abroad, and a recent article by Quénu and Perol summarizes these. In 5 of the 6 cases paraffin or vaseline was injected beneath the skin of the penis in order to enlarge the organ. This artificially induced hypertrophy was a total failure, as all 5 patients lost the power of erection until operated upon and the tumor tissue excised. In the sixth case no definite history of injection could be obtained, but the authors believe this to have been the case.

The case to be presented herewith is unique in that a paraffinoma of the penis developed as the result of the external application of petrolatum concurrently with occupational exposure to a cutting oil.

CASE REPORT

A white man, aged 33, admitted on October 31, 1947, complained of a swollen penis. Eleven months previously, after a deer hunting trip, he had noticed an irritation of his foreskin which he attributed to the chafing of his long woolen underwear. The foreskin was abraded on the right dorsal aspect and a serous exudate came from this point. He applied petrolatum and a gauze bandage, but the lesion did not heal. The prepuce became swollen, and retracted from the glans. Later the skin of the shaft became swollen and hard. He applied petrolatum bandages daily for the next 6 months, occasionally substituting icthyol ointment. Four large size bottles (approximately 4 ounces each) of petrolatum and 1 small tin of icthyol were thus consumed. At times the skin of the prepuce would seem to heal, but then it would break down again, discharging a small amount of pus. He abstained from sexual intercourse although erections continued to occur. Because of pain in his groins he visited his family doctor after 6 months. Ammoniated mercury ointment and hot soaks were tried with no discernible effect. A course of penicillin was also given without benefit. He continued to use hot soaks, and the condition remained unchanged for the next 4 months. He was otherwise in good health.

The past history was not remarkable. He denied venereal disease or exposure. His wife and children were in good health.

He had been employed as a machinist and lathe operator for 7 years by a ball bearing manufacturing concern. In his work he was constantly splashed by cutting oils. Although his clothing was rarely saturated with this oil, enough was constantly present to impart a stain and odor to his underclothes even after laundering. Oil acne occasionally developed on his body after especially marked exposure.

Physical examination was generally normal save for the penis and inguinal regions. The entire shaft of the penis was enlarged to twice normal size by a subcutaneous thickening which was hard, fixed and nontender. The skin of the penis was pale, nonelastic, and capillary circulation seemed poor. The prepuce had been retracted by the swelling to the level of the corona. The mucocutaneous junction of the prepuce was cracked and slightly infected in several places. The glans was uninvolved and appeared normal. The tumor tissue extended a few centimeters into the subcutaneous tissue of the abdomen surrounding the base of the penis. Bilateral rubbery inguinal nodes were present. The follicles of the skin of the thighs and forearms were filled with small black plugs, but were uninflamed.

Urinalysis was normal. Hemoglobin was 15.5 gm. per cent. The red blood cells numbered 4.98 million. The white blood cell count was 6,400 with 50 per cent neutrophiles, 43 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophiles and 3 per cent baseophiles. The Kahn and Kolmer tests were negative on two specimens of blood. The Frei test and tuberculous patch tests were negative.

On October 31, 1947, biopsies of the skin and subcutaneous tissue of the penis were taken under sodium pentothal anesthesia. A lymph node was also removed from the left groin. The tumor tissue was noticeably avascular and bleeding was almost absent. The penile wounds failed to heal and broke down during the ensuing week. A diagnosis of paraffinoma of the penis was returned following microscopic examination. See figure 1.

On November 7, 1947 excision of the paraffinoma was performed. Spinal anesthesia was given. A circular incision was made on the distal shaft of the penis and a cleavage line found just under the skin. The entire skin of the shaft was then reflected proximally, exposing the firm, whitish friable subcutaneous tissue which constituted the body of the tumor. This was then dissected off. A good cleavage line was found at the level of Buck's fascia, and the latter was seen to be healthy and not involved. The tumor tissue was removed in its entirety up to the mucosa of the coronal sulcus, and a circumcision was performed. The penile skin was then pulled forward and reunited to the mucosa of the coronal sulcus, thus forming a full thickness graft. A pressure dressing was applied.

Following operation the patient was comfortable and the wound remained healthy save for a small area on the under side of the penis near the frenulum.

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Following operation the patient was comfortable and the wound remained healthy save for a small area on the under side of the penis near the frenulum.

A triangular area approximately 2 by 1 by 1.5 cm. sloughed. Healthy granulation tissue appeared here by the time of discharge on the eleventh postoperative day. During the next few weeks this area epithelialized slowly, and there was some question as to whether a skin graft would be necessary. Marital relations were resumed at this point, and a perfect functional result was reported. Surgery was therefore deferred. A mild cellulitis later occurred, necessitating re-admission from December 19, 1947 to December 22, 1947, for treatment with penicillin, sulfadiazine, and compresses. The infection quickly subsided, the remaining induration disappeared, and the penis shrank to its normal size within another month. At follow-up examination in February 1949, the appearance was normal, and the patient was satisfied with its function. A small amount of tumor tissue was still present under the skin of the abdomen at the base of the penis, but no inconvenience is caused by it.

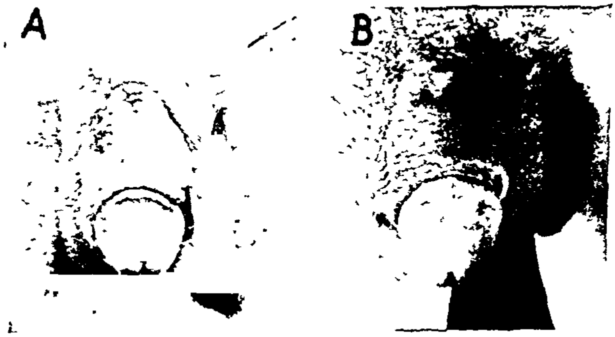

FIG. 1. *A*, paraffinoma of penis following biopsy. Note whitish tumor tissue which has caused retraction of prepuce. *B*, result 3 months after excision of paraffinoma of penis.

The operative specimen consisted of a strip of tissue measuring 10 by 4 by 1 cm. and weighed 24 gm. The cut surface had a yellow spongy appearance, was rubbery in consistency, and exuded droplets of oily fluid under slight pressure.

Section showed the epidermis to be atrophic. The underlying tissue had a spongy appearance, being composed of vacuoles of varying sizes. The interstitial tissue was avascular and showed fibroblasts, pale staining fibrous tissue, and occasional large mononuclear cells at the periphery of the small sized vacuoles. Foci of lymphocytes and plasma cells were noted in the deeper tissue.

Section of the inguinal node removed at biopsy showed the architecture to be disrupted by numerous large and small vacuoles throughout the parenchyma. Here and there large lipophages were noted alongside the smaller vacuoles. A few multinucleated giant cells were seen in juxtaposition with the larger vacuoles. The giant cells contained small vacuoles in their cytoplasm. See figure 2.

An attempt was made to identify the oil responsible for the tumor formation by staining sections of tissue with various fat stains. Scarlet R stain on the lymph node showed an affinity for the vacuoles. Scarlet R is not a specific stain as it will stain animal, vegetable, and mineral oils. Ikeda used scarlet R in his studies of lung paraffinomas, stating that the oil globules that stained yellow to orange were of mineral origin.

Osmic acid is reduced to black osmic hydroxide by the action of fatty acids, and is therefore used for staining neutral fats. A section of the tumor tissue was stained with osmic acid. No reduction of the stain occurred, indicating that the oil in the tissue was not a neutral fat. A control section of normal human fat and muscle showed reduction of the osmic acid by the fat.

In a further attempt to identify the oil as being of mineral origin a saponification procedure was done. Mineral oil is a saturated hydrocarbon containing no fatty acids, and accordingly is nonsaponifiable. The saponification number of the oil expressed from the operative specimen was 9. The saponification number of the oil expressed as a control from human fat was 118. Human fat theoretically has a saponification number of 180. This indicates that the oil in the tumor tissue was not of human origin.

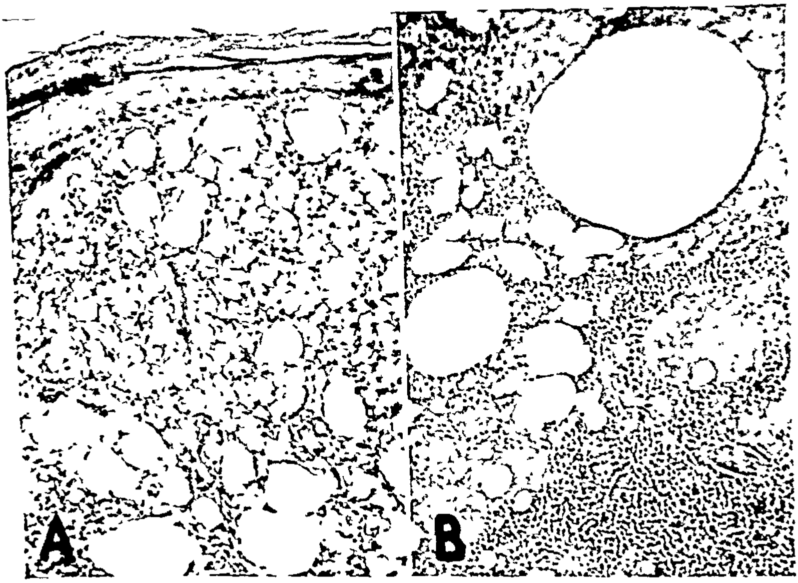

FIG. 2. *A*, photomicrograph (low power) of paraffinoma removed at biopsy. Vacuoles containing mineral oil begin immediately beneath skin. *B*, photomicrograph (high power) of lymph node from inguinal region.

Final proof of the extrinsic source of the oil contained in the operative specimen was obtained by submitting it to infra-red spectroscopy. This indicated it to be a saturated paraffin hydrocarbon, and therefore mineral in origin.

DISCUSSION

Although it is possible to show with reasonable certainty that the oil in the excised tissue was of mineral origin the mechanism of its introduction remains uncertain. The patient had been exposed to cutting oils in his work for 7 years, but disclaimed appearance of the tumor until he applied petrolatum to his penis during a period of 6 months. The irritating qualities of cutting oils were well known to him. He suffered more or less continuously from a folliculitis of the legs due to it. In 1942 when some new types of cutting oil were introduced because of war shortages, both he and his fellow workers developed extensive rashes of the body and legs. On the other hand a patch test made with the cutting oil currently used in his work was negative.

That petrolatum alone could produce such a lesion seems highly unlikely. This substance has long been used as a dressing for granulated or denuded areas, and paraffinoma formation from this use has never been reported. Furthermore, mineral oil compounds are in constant daily use by a large proportion of the population either as lipstick, which contains 15 to 25 per cent petrolatum, or hair dressings, which contains up to 95 per cent petrolatum. Skin reactions to these compounds are practically unknown. A research consultant of a large petrolatum manufacturing company stated that no such reaction to the topical application of petrolatum had previously been reported to them.

It seems likely that the combination of the cutting oil and petrolatum on an abrasion may have been responsible for the absorption which occurred. Cutting oils are essentially emulsifying agents, and are therefore water miscible. These qualities would certainly favor the penetration of petrolatum into an abraded surface if not into the skin itself. No experiments to test this have been carried out. The patient admitted that his hands were very apt to be covered with oil when he went to urinate while at work and that his overalls were often saturated with the cutting oil. There is no doubt that ample opportunity was thus afforded for sufficient cutting oil to mix with the petrolatum dressing to produce both emulsification and penetration.

SUMMARY

A case of paraffinoma of the penis is reported due to topical application of petrolatum concurrently with occupation exposure to cutting oils. The mineral nature of the oil in the tissues has been corroborated by fat stains, saponification procedures, and infrared spectroscopy. No previous case of paraffinoma following external application of petrolatum has been recorded.

Grateful acknowledgment is made to Charles A. W. Uhle, M.D., chief of the Department of Urology, Lankenau Hospital, for permission to report this case, and to Clark E. Brown, M.D., chief of the Department of Pathology, Lankenau Hospital, for his assistance and encouragement in the preparation of this paper.

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REFERENCES

Benedek, L.: Die paraffinome. Pester Med. Chir. Presse, **49:** 221, 1913.

Council on Foods and Nutrition of American Medical Association. Report of: Mineral oil in foods. J. A. M. A., **123:** 967, 1943.

Committee on Occupational Dermatoses of the American Medical Association. Report of: Industrial dermatitis; special reference to oil dermatitis. J. A. M. A., **122:** 370, 1943.

Cornbleet, T. and Popper, H. L.: Properties of human skin revealed by fluorescence microscopy—paraffinoma. Arch. Dermat. & Syph., **47:** 637, 1943.

Gersuny, O.: Uber eine subkutane prothese. Ztschr. f. Heilkunde, **9:** 1, 1900.

Heidingsfeld, M. L.: Histopathology of paraffin prosthesis. J. Cutan. Dis., **24:** 513, 1906.

Ikeda, K.: Lipoid pneumonia of adult type. Paraffinoma of the lung. Report of 5 cases. Arch. Path., **23:** 470, 1937.

Mason, M. L. and Queen, F. B.: Grease gun injuries to hand. Pathology and treatment of injuries (oleomas) following injection of grease under high pressure. Quart. Bull. Northwestern Univ. Med. School, **15:** 122, 1941.

ORMSBY, O. S. AND MONTGOMERY, H.: Diseases of the Skin. Philadelphia: Lea & Febiger, 1943, pp. 882–885, 6th ed.

QUÉNU, J. AND PEROL, E.: Paraffinomas of the penis. J. Chir. Par., **63:** 345, 1947. Abstracted in Int. Abstr. Surg., **86:** 174, 1948.

SCHNEIDER, L.: Pulmonary hazard of ingestion of mineral oil in apparently healthy adult. Report of 5 cases. New Eng. J. Med., **240:** 284, 1949.

STRYKER, W. A.: Absorption of liquid petrolatum (mineral oil) from the intestine. A histologic and chemical study. Arch. Path., **31:** 670, 1941.

WHITAKER, W. G. JR., WALKER, E. T. AND CANIPELLI, J.: Lipogranuloma of peritoneum. Report of 3 cases following intra-abdominal use of liquid petrolatum. J. A. M. A., **138:** 363, 1948.

WHITEWELL, G. P. B.: Dermatitis from cutting oils. Lancet, **2:** 493, 1943.

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CARCINOMA OF COWPER'S GLAND

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Carcinoma of Cowper's gland origin is rare. Since Mery's brief description of the glands in 1684 and Cowper's more complete study in 1704, only 6 cases of proven primary carcinoma of this organ have appeared in the literature. Paquet and Hermann presented the first recorded case in 1884. Then followed the cases of Pietrzikowski and Gussenbauer in 1885, and Kocher in 1886. C. Kaufman compiled these first 3 cases. The next reported cases were those of Di Maio in 1928, and Uhle and Archer in 1935. Gutierrez collected all cases up to 1937, including a case of his own confirmed by surgery and biopsy. None of the above 6 cases were studied at autopsy. E. Kaufman refers to an adenocarcinoma in the perineum which he felt originated from Cowper's glands. This would represent the seventh case. To these we wish to add the eighth case of primary carcinoma of Cowper's glands.

CASE REPORT

A 66 year old white man was admitted on February 7, 1949 in complete urinary retention. He had a 4 year history of progressive urinary difficulty culminating in a 4 month period of marked frequency and nocturia. For 1 week before the acute episode he had had paradoxical incontinence and a distended bladder. This was associated with bilateral ankle edema. He had been under the care of his family physician for cardiac complaints for some time. He gave a past history of hypertension, but there was no weight loss, anorexia, or melena. There was no family history of carcinoma. The patient admitted heavy alcohol intake. He denied venereal disease. The general physical examination revealed a well developed and well nourished white man with a slightly enlarged heart and frequent extrasystoles. The ankle edema disappeared in a few days and his general condition improved rapidly with digitoxin and mercupurin.

The bladder was palpable two fingers above the umbilicus and bilateral ankle edema was present. The external genitalia were normal. Externally a prominence was seen in the perineum and a mass, approximately three centimeters in size, was palpable. On rectal examination the mass could be grasped between the rectal finger and the thumb on the perineum. It was located at the level of the urogenital diaphragm and extended distally along the penile urethra. Continuous with the mass was a nodule, 1 cm. in diameter, which was at this time considered to be intrinsic within the apex of the prostate. The prostate was 1 plus enlarged, smooth, movable, nontender and of normal consistency except for the nodule mentioned.

The patient was placed on indwelling catheter drainage and 2800 cc clear urine was removed initially. A diagnostic study was negative for disease of the chest or bowel. An excretory urogram showed only slight left ureteropyelectasia.

On cystopanendoscopy, moderate trabeculation and cellule formation in the bladder, and a minimally enlarged nonobstructing prostate were observed. Two centimeters distal to the external sphincter there was a zone of nodularity about 0.5 cm. in length, intruding into the urethra. The panendoscope was grasped tightly at this point.

After reflecting the skin and superficial fascia at operation, an ovoid, symmetrical mass appeared in the midline of the perineum. The mass was fixed, firm and very hard. It apparently occupied the superficial perineal space and extended forward around the urethra to involve the posterior portion of the bulbocavernosus. The diameter of the exposed mass was just less than 3 cm. It seemed to extend deeply into the perineum to involve the urogenital diaphragm. The prostate was found to be free and *not* fixed to the mass. The small nodule, originally thought to occupy the apex of the prostate, was in the midline and was definitely fixed to and formed part of the tumor. Further exposure to identify it as Cowper's gland was not carried out. Resection was not attempted at this time, but a biopsy from the mass proper was taken. The pathological diagnosis by Dr. A. Angrist was "Perineum: adenocarcinoma, origin questionable." The section showed the histologic structure of mucogenic adenocarcinoma mindful of rectal or colonic cancer. The nodules observed previously in the anterior urethra were resected with the Stern-McCarthy resectoscope. This urethral biopsy was "fibro-fatty tissue, vessels, nerves and striated muscle, chronic inflammation and foreign body giant cells."

His postoperative course was uneventful. The urethral catheter was removed on the sixth day and he voided with ease thereafter. The residual urine amounted to 20 cc. Two acid phosphatase determinations were 2.8 and 3.0 King-Armstrong units. These findings and the continuity of the mass with the apex of the prostate suggested the original clinical diagnosis of primary adenocarcinoma of the prostate. He was discharged on March 4, 1949 on stilbesterol. The mucogenic appearance of the tumor prompted the pathologist to list the tumor as adenocarcinoma of the perineum, rather than of the prostate. This subtlety was apparently lost and the patient was subsequently treated as a case of adenocarcinoma of the prostate.

In spite of stilbesterol therapy, eventual ulceration of the skin of the perineum occurred. Observation in the outpatient department recorded progressive increase in the size of the mass during the following months, with extension of the growth along the anterior urethra for about 6 cm. Acute retention was never again a prominent feature and he voided freely through the anterior urethra until his final admission. He complained at this time of severe pain in the region of the mass. A bilateral orchiectomy was performed in the hope of slowing the growth of the presumed prostatic cancer. Histologically, the testicles showed complete absence of spermatogenesis, marked atrophy and hyalin thickening of the basement membrane. No hyperplasia of Leydig cells was noted.

His final admission occurred on March 5, 1950 when he was admitted in acute left cardiac failure. At this time there was a fistula in the ulcerating perineal mass, through which he was voiding all his urine. No sound could be passed through the anterior urethra, or through the perineal fistula, into the bladder. His bladder was not palpable however, and he was completely continent. His blood urea remained within normal limits at all times, but he finally succumbed to cardiac failure and general debility, dying on April 17, 1950, twenty-five months after his first admission.

At autopsy, the body was that of a fairly well preserved, elderly white male. Over the anterior perineum there was noted a large, fungating growth, which measured 5 cm. in diameter and protruded 3 cm. above the skin surface. The adjacent perineal skin extended over the sides of the mass, and the skin was thickened, indurated and erythematous. The surface of the mass showed extensive necrosis and suppuration. In the center there was a draining sinus which was found to communicate directly with the membranous urethra, admitting a 3 to 4 mm. probe. Anteriorly there was considerable induration and fluctuation. The scrotal sac was uninvolved. The posterior perineum and anal region were not remarkable and showed no evidence of tumor invasion. Dissection of the lower urinary tract showed the superficial perineal pouch to be filled with bulky, necrotic, neoplastic tissue continuous with the mass noted externally. In the center of the mass there was an abscess cavity filled with pus and necrotic debris. The cavernous urethra, bulb and Cowper's glands could not be identified, presumably having been completely replaced by tumor tissue. Despite the marked tendency to local invasion, there was no extension upwards through the upper layer of the urogenital diaphragm, which appeared to have acted as a limiting plane. A line of resistance posteriorly was also noted, suggesting a

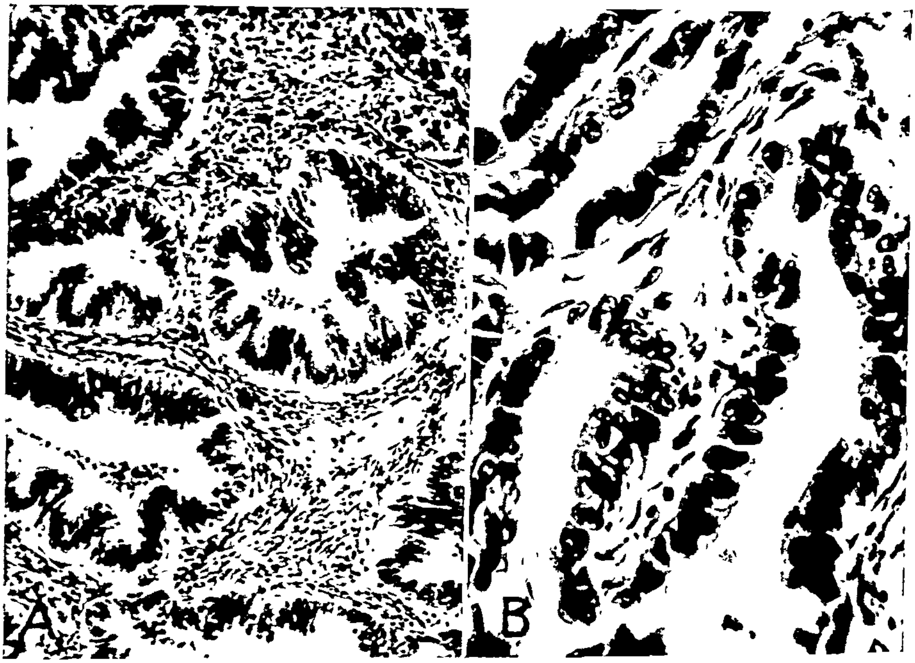

FIG. 1

limiting barrier, formed by the fusion of Colles' fascia to the posterior margin of the urogenital diaphragm. The pelvic viscera were freely movable, showing no evidence of fixation or tumor infiltration. There was a natural line of cleavage along Denonvilliers' fascia. The prostate was small, and showed no gross evidence of tumor, either primary or secondary. The bladder was filled with purulent, infected urine, and there was a hemorrhagic cystitis. The prostatic urethra was similarly injected. No evidence of urinary tract obstruction was seen at any point, or evidence of ascending infection beyond the bladder. No pelvic or inguinal lymph node metastases were found. The remainder of the autopsy revealed no significant findings other than arteriosclerotic heart disease. The gastro-intestinal tract showed no evidence of neoplasm, and the rectum was free and clear.

Histologic sections (fig. 1) of the mass showed fairly well differentiated glandular structure displaying high columnar epithelium with frequent papillary infoldings. No secondary lumen formation, such as is seen so commonly in large bowel cancers, was present. Mucus was found filling and distending many gland lumina. Numerous mitotic figures were present. A tubular and glandular structure was maintained throughout. The tumor showed a moderate scirrhous reaction and a marked tendency to local invasion without a delimiting capsule. The overlying perineal epidermis showed an irritative papillary hyperplasia. Other areas of the tumor showed extensive necrosis and suppuration. Sections of the tumor taken at autopsy resembled exactly those of the surgical biopsies.

DISCUSSION

Because of the anatomical location and the histology of the tumor, the primary site of origin in this case is believed to be Cowper's glands. It is significant that continuity with no adjacent tissues from which a glandular tumor of this type might arise could be established. The prostate is ruled out as a possible source of this neoplasm by the location of the tumor and the histologic appearance, which is at variance with cancers of this organ, and further by the fact that the prostate showed nothing but minimal benign hypertrophy on gross and microscopic examination.

The most important differentiation, however, is that of distinguishing primary carcinoma of the urethra from carcinoma originating in Cowper's glands with secondary involvement of the urethra. Both lesions are strikingly similar in their clinical manifestations. The typical carcinoma of the perineal urethra, according to Kreutzmann and Colloff, also presents as a perineal tumor commonly showing secondary infection and necrosis. There is eventual ulceration with the development of persistent urinary fistulas, which are refractory to surgical cure. Prior to the appearance of the perineal mass, the patient invariably has already had well established symptoms of urinary difficulty. Commonly (76 per cent according to Kreutzmann and Colloff), there is a preceding history of stricture. Carcinoma of Cowper's gland likewise makes its appearance as a perineal mass with associated discomfort and pain in the region of the perineum and rectum. Characteristic, however, as pointed out by C. Kaufmann, is the failure of urinary symptoms to become manifest until relatively late in the course of the disease. This is in contrast to primary lesions of the urethra, which, as noted, present first in the form of urinary difficulty with the later development of a perineal mass.

The present patient was entirely unaware of the existence of the perineal mass at the time of the original admission with urinary retention. The tumor process was found well advanced, but no exact estimate of its duration can be established. Its histological pattern would suggest a tumor of slow growth.

Pathologically the problem of differential diagnosis is not so difficult. The majority of carcinomas of the male urethra are squamous cell cancers. Glandular carcinomas occur extremely rarely. Their origin is usually from the glands of Littré or the lacunae of Morgagni in the penile portion of the urethra. In the 148 cases of carcinoma of the male urethra collected by Kreutzmann and Colloff there were only four of glandular structure, and these were all confined to the penile urethra.

A case was reported by Allenbach in 1916 of carcinoma of the urethra in a 51 year old man. This case is of special interest and merits some comment. It was included among the reviewed cases of Kreutzmann and Colloff as the single instance of columnar cell carcinoma. It showed columnar cell masses with scattered gland formation (*cylindrocellularen Krebszapfen mit vereinzelter Drüsenbildung*). Although the exact anatomic site of the primary lesion was not specified, the impression imparted from the description is that the principal locus was the bulbous portion of the cavernous urethra with extension anteriorly from this point. No invasion upwards through the triangular ligament had occurred, and the prostate was uninvolved. This lesion had metastasized widespread at autopsy to involve regional nodes, liver and lung. This is the only case ever reported of a glandular carcinoma originating in this portion of the urethra. It raises the question as to whether this tumor does not represent an additional case of Cowper's gland carcinoma. The gross features bore striking similarities to other proven cases of Cowper's gland cancer.

Blanc, Wies and Carret in 1910 reported a case clinically diagnosed as carcinoma of Cowper's glands which had clinical features closely simulating other known cases of this disease. Their case, however, was not corroborated by histologic study or surgical intervention.

A tumor similar to this tumor histologically does originate in the bladder. The urachus and cystitis cystica have been implicated as sources of origin. In this instance the bladder did show severe cystitis, but no involvement by tumor, and no tumor was seen locally in the bladder at the time of the original cystoscopic examination.

The problem of ruling out a primary tumor of the urethra remains. The theoretical possibility exists that a mucogenic tumor might arise from the membranous or bulbous portions of the urethra following an equivalent urethritis cystica or urethritis glandularis metaplasia. In view of the naturally existing mucus secreting Cowper's gland epithelium, this seems improbable. In the case presented here the urethra was examined visually with a panendoscope and showed no evidence of primary tumor at a stage of the disease when the tumor already measured fully 3 cm. in diameter.

The marked resemblance histologically to rectal adenocarcinoma was a striking feature. The location of the tumor with its differentiated, mucogenic, glandular structures actually suggested a primary origin in the colon or rectum on surgical biopsy. This tumor presents, therefore, the problem of differential diagnosis of rectal carcinoma on both clinical and histologic grounds. In this connection it is noteworthy that the case reported by Gutierrez had been previously diagnosed and treated as internal hemorrhoids, and that the patient had actually undergone various operative procedures on the rectum and anus. The case reported by Uhle and Archer had also been treated for fistula in ano before the correct diagnosis was made.

The fascial limitations in their relation to the tumor growth in this case are of particular anatomical significance. In Gutierrez's case distinct fascial limitation was also present, Denonvilliers' fascia acting as a limiting barrier in preventing posterior extension of the tumor. The urogenital diaphragm also appeared to act as a limiting structure in our case. The case of Allenbach suggests similar anatomical limitations on the basis of the data given.

Though some variation exists in the fascial thickness of the urogenital diaphragm, Young has noted that the deep fascial layer of the triangular ligament is usually thinner than the superficial layer. The spread of the tumor anteriorly requires, therefore, some explanation. At the initial examination the anatomic relationships were consistent with a spread through the hiatuses in the inferior layer where the excretory ducts of Cowper's glands penetrate. Possibly more important is the effect of muscular action and the transmission of intravesical and intra-abdominal pressure during micturition, which directs the tumor mass outward by physical forces. Though this might not influence direction of growth per se, the thrusting of the bulk of the mass outward and downward can be effected by such forces.

When this case came to our attention, the patient had already passed the early stage of the disease and the growth had extended along the anterior urethra. It is of interest to note that the urethral mucosa was not involved at this time in spite of the extent of the neoplasm around it. After the transurethral resection of the intra-urethral nodules the patient was never again stricken with urinary retention. In spite of the progressive growth of the tumor mass, which subsequently invaded the anterior urethra, acute retention did not occur because of the development of a perineal fistula which diverted the urinary stream. The continued control of micturition, which lasted to the very end, was striking, in view of the strategic location of the tumor.

SUMMARY AND CONCLUSION

A case of carcinoma of Cowper's gland, studied at autopsy, is presented. The only other instance of probable carcinoma of Cowper's gland studied at autopsy was that of Allenbach, and this was interpreted as primary in the urethra proper.

The possible sites of origin of glandular tumors in this location are discussed.

The difficulties encountered in establishing the diagnosis are noted and evaluated in their clinical, anatomic and pathologic features. The initial location, the glandular and mucogenic histological pattern, as confirmed at operation; the limitation of extension found to correspond with known anatomical fascial planes and the elimination of other regional sites of origin, as confirmed at autopsy, seem to establish the diagnosis of Cowper's gland cancer in this instance.

There is an inadequate follow-up of the cases collected to permit an authoritative statement as to prognosis. On the basis of the slow course and the absence of metastasis at autopsy in this case, an heroic attempt at surgical extirpation would seem to be an indicated procedure.

REFERENCES

ALLENBACH, E.: Primäres Urethralcarcinom mit priapusähnlichen Folgen. Deutsche Ztschr. f. Chir., **138**: 152, 1916-17.

BLANC, WIES AND CARRET: Cancer of Cowper's glands . La Loire Mèdicale, **29**: 375, 1910.

GUTIERREZ, R.: Primary carcinoma of Cowper's gland. Surg., Gynec. & Obst., **65**: 238, 1937.

KAUFMANN, C.: Deutsche Chirurgie, Lief. 50a, Stuttgart, 1886.

KAUFMANN, E.: Pathology. Philadelphia: A. Blakiston's Son & Co., 1929.

KREUTZMANN, H. AND COLLOFF, B.: Primary carcinoma of the male urethra. Arch. Surg., **39**: 513, 1939.

UHLE, C. A. W. AND ARCHER, G. F.: Primary carcinoma of Cowper's glands. J. Urol., **34**: 128, 1935.

YOUNG, H. H. AND DAVIS, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders, Co., 1926.

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SPERM SURVIVAL AT ESTIMATED OVULATION TIME: COMPARATIVE STUDIES IN MORPHOLOGY

A PRELIMINARY REPORT

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Most physicians who have interested themselves in the problem of sterility have established and utilized criteria for the evaluation of the infertile couple. The minimal standards of procedure have always included sperm examination obtained both by the Sims-Hühner post-coital method and by ejaculation or withdrawal. To properly evaluate fertility in the male, it is no longer sufficient to examine a specimen, note a number of actively motile sperm, and thus prognosticate that such sperm are capable of fertilization. Morphological studies must be made, since there is now evidence that a high percentage of abnormal forms is indicative of male sterility. In addition, the investigator must know whether the normal appearing spermatozoa are able to penetrate cervical mucus at the time considered optimal for impregnation. At ovulation time the cervical mucus becomes profuse, thin and glairy, and motile spermatozoa are routinely recoverable for as long as 72 hours post-coitus at this phase of the menstrual cycle.

In a previous report, we concluded that even with maximal sperm survival in the cervical mucus, one cannot prognosticate fertilization of the ovum. During the discussion which followed this report, two questions were raised: 1) Are those motile sperm remaining 24 to 72 hours post-coitus capable of fertilizing an ovum? 2) What is the morphology of spermatozoa surviving in cervical mucus? To our knowledge, no report has ever been made wherein sperm-containing mucus aspirated from the endocervix was used for artificial insemination in humans or in animals. Thus it is not now possible to answer the first query. This present study was undertaken in an attempt to answer the second question.

METHOD

A group of 16 patients were seen daily, so that the time of ovulation could be estimated by: 1) basal body temperature; 2) vaginal smear; and 3) character of the cervical mucus. Coitus was advised a) when the basal temperature was at the lowest point; b) when the vaginal smear pattern was just short of complete cornification; and c) when the cervical secretions became more fluid. When the results of the three methods were at variance, greatest reliance was placed upon the character of the cervical mucus. It has been our experience that the presence of an excessive amount of thin, clear cervical secretion is reliable evidence of ovulation. Also, we placed the greatest credence in this characteristic finding inasmuch as it is objective evidence, independent of possible error by the patient in reading and recording basal body temperature. When ovulation time was thus determined, the patient was instructed to report at various intervals

The difficulties encountered in establishing the diagnosis are noted and evaluated in their clinical, anatomic and pathologic features. The initial location, the glandular and mucogenic histological pattern, as confirmed at operation; the limitation of extension found to correspond with known anatomical fascial planes and the elimination of other regional sites of origin, as confirmed at autopsy, seem to establish the diagnosis of Cowper's gland cancer in this instance.

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REFERENCES

ALLENBACH, E.: Primäres Urethralcarcinom mit priapusähnlichen Folgen. Deutsche Ztschr. f. Chir., **138:** 152, 1916–17.

BLANC, WIES AND CARRET: Cancer of Cowper's glands . La Loire Mèdicale, **29:** 375, 1910.

GUTIERREZ, R.: Primary carcinoma of Cowper's gland. Surg., Gynec. & Obst., **65:** 238, 1937.

KAUFMANN, C.: Deutsche Chirurgie, Lief. 50a, Stuttgart, 1886.

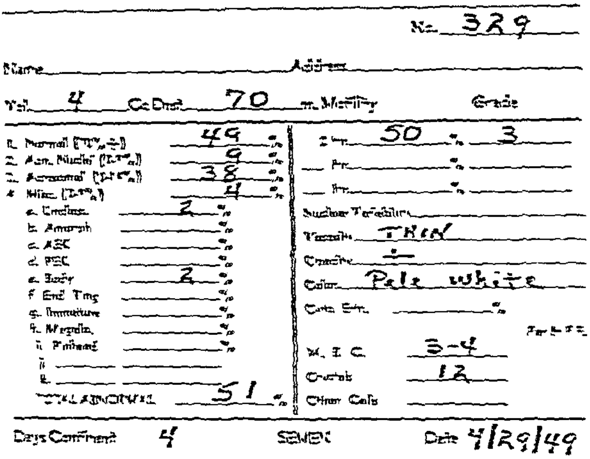
KAUFMANN, E.: Pathology. Philadelphia: A. Blakiston's Son & Co., 1929.

KREUTZMANN, H. AND COLLOFF, B.: Primary carcinoma of the male urethra. Arch. Surg., **39:** 513, 1939.

UHLE, C. A. W. AND ARCHER, G. F.: Primary carcinoma of Cowper's glands. J. Urol., **34:** 128, 1935.

YOUNG, H. H. AND DAVIS, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders, Co., 1926.

lowed to air dry. These smears were flamed and stained with gentian violet and rose bengal, according to the method of Williams (fig. 1). They were then examined under the oil immersion lens, and a minimum of 300 spermatozoa were classified morphologically, as in semen analysis (fig. 2). The morphology of spermatozoa obtained at post-coital examination was compared with the analysis of semen previously obtained by friction or coitus interruptus.



No. 329

Name ______ Address ______

Vol. 4 Ct. Dnst. 70 m. Motility ______ Grade ______

1. Normal (70%±)	49 %	1 hr. 50 %	3
2. Abn. Nuclei (15%)	9 %	__ hr. __ %	
3. Acrosomal (15%)	38 %	__ hr. __ %	
4. Misc. (10%)	4 %	[illegible]	
a. Coiled	2 %	Viscosity	THIN
b. Amorph	%	Coagulation	±
c. ABC	%	Color	Pale white
d. PEC	%	Cells Str.	%
e. Body	2 %		Per h.p.f.
f. End Tag	%	W. B. C.	3-4
g. Immature	%	Crystals	12
h. Megalo.	%	Other Cells	
i. Pinhead	%		
j.			
k.			
TOTAL ABNORMAL	51 %		

Days Continent 4 SEMEN Date 4/29/49

Fig. 2

TABLE 1

Semen analysis

NO.	PRIM. OR SEC.	VOL. CC.	COUNT	% MOTILITY	GRADE	TOTAL ABNORMAL	ABNORMAL NUCLEI	ACROSOMES	MISCEL-LANEOUS
331	P	5	45	27%	II	19%	1%	6%	12%
322	P	3	89	80	IV	14	2.3	7	4.7
312	P	5	211	90	IV	7	4	2	1
325	P	7	46.5	60	III	19.3	11.3	6	2
319	S	4	119	40	II, III	11	1	6	4
270	S	6	84	90	IV	5	1	3	1
378	P	8	210	60	IV	7	0	4	3
276	P	4	40	60	III	29	3.5	20	5.5
334	S	3	88	80	IV	7	?	?	?
329	P	4	70	50	III	51	9	38	4
275	P	4	66	60	III, IV	17	6	10	1
317	P	5	57	60	III	21	4	14	3
332	P	5	185	80	III	20	?	?	?
324	P	4	60	60	III	42.3	2.9	32.5	6.9
377	P	4	214	84	III	14	0.5	5	8.5
272	P	4	187	70	III	27.3	18.3	2	7

RESULTS

A group of 16 couples, 13 of whom were classified as primary sterility and 3 of whom complained of secondary sterility, were selected for this study. The group was necessarily limited to those women in whom post-coital examination of time for post-coital examination. Specimens of cervical mucus were obtained by aspiration from the endocervix, using a glass cannula having a goose neck tapering tip (Cary cannula). Grading of scant, 1 plus, to profuse, 4 plus, was tabulated. Viscosity was designated as thick, moderate or thin. The material was placed on a glass slide and examined immediately under the microscope for the presence of spermatozoa. The average number per high power field, as well as the grade of motility, were noted. The grade of motility was designated thus:

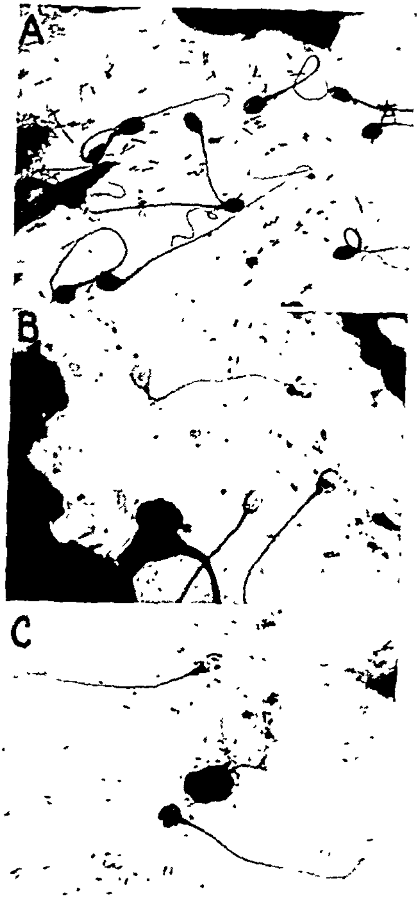
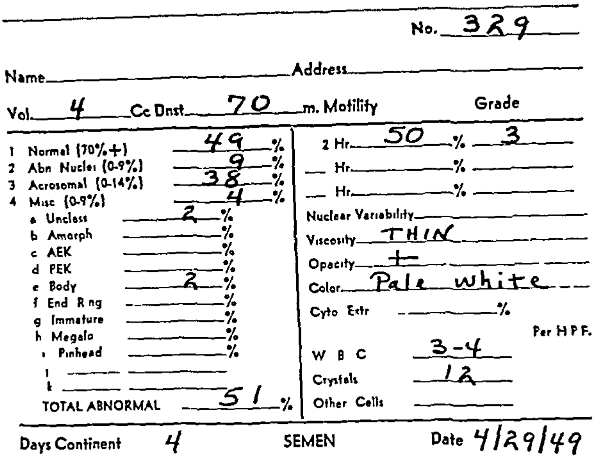


FIG. 1. *A*, cervical mucus containing spermatozoa 12 hours post-coitus. All normal forms. Case No. 322. *B*, spermatozoa surviving in cervical mucus 38 hours post-coitus. All forms shown are normal. Case No. 319. *C*, two abnormal spermatozoa surviving in cervical mucus 14 hours post-coitus. Case No. 276.

Grade 0	No motility
Grade 1	Slight undulations
Grade 2	Sluggish motion
Grade 3	Moderate motility
Grade 4	Active forward progression

Thin smears of the mucus containing spermatozoa were then made and allowed to air dry. These smears were flamed and stained with gentian violet and rose bengal, according to the method of Williams (fig. 1). They were then examined under the oil immersion lens, and a minimum of 300 spermatozoa were



No. 329

Name ____ Address ____

Vol. 4 Cc Dnst. 70 m. Motility Grade

1 Normal (70%+) 49 %
2 Abn Nuclei (0-9%) 9 %
3 Acrosomal (0-14%) 38 %
4 Misc (0-9%) 4 %
a Unclass 2 %
b Amorph ____ %
c AEK ____ %
d PEK ____ %
e Body 2 %
f End Ring ____ %
g Immature ____ %
h Megalo ____ %
i Pinhead ____ %
j ____ ____
k ____ ____
TOTAL ABNORMAL 51 %

2 Hr. 50 % 3
__ Hr. ____ % ____
__ Hr. ____ % ____
Nuclear Variability ____
Viscosity THIN
Opacity +
Color Pale white
Cyto Extr ____ %
Per HPF.
W B C 3-4
Crystals 12
Other Cells ____

Days Continent 4 SEMEN Date 4/29/49

FIG. 2

TABLE 1

Semen analysis

NO	PRIM OR SEC.	VOL C C	DNST M	2 HOUR MOTILITY	GRADE	TOTAL ABNORMAL	ABNORMAL NUCLEI	ACROSOMES	MISCELLANEOUS
351	P	5	46	20%	II	19%	1%	6%	12%
322	P	3	89	80	IV	14	2.3	7	4 7
302	P	5	201	90	IV	7	4	2	1
325	P	7	46 5	60	III	19.3	11 3	6	2
319	S	4	119	40	II, III	11	1	6	4
400	S	6	84	90	IV	5	1	3	1
398	P	8	210	60	IV	7	0	4	3
276	P	4	40	60	III	29	3.5	20	5.5
304	S	3	83	80	IV	7	?	?	?
329	P	4	70	50	III	51	9	38	4
275	P	4	66	60	III, IV	17	6	10	1
307	P	5	30	60	III	21	4	14	3
332	P	5	195	80	III	20	?	?	?
324	P	4	60	60	III	42 3	2.9	32.5	6.9
377	P	4	204	80	III	14	0.5	5	8.5
279	P	4	107	70	III	27.3	18.3	2	7

classified morphologically, as in semen analysis (fig. 2). The morphology of spermatozoa obtained at post-coital examination was compared with the analysis of semen previously obtained by friction or coitus interruptus.

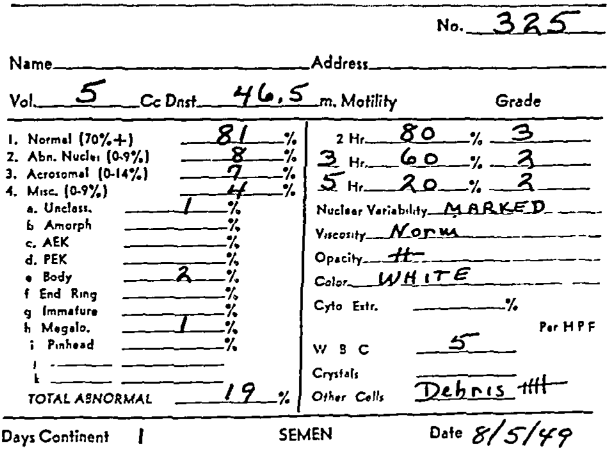
RESULTS

A group of 16 couples, 13 of whom were classified as primary sterility and 3 of whom complained of secondary sterility, were selected for this study. The group was necessarily limited to those women in whom post-coital examination revealed spermatozoa numerous enough for adequate morphological studies. Specimens of mucus were obtained from 1½ to 38 hours post-coitus, a mode of 14 hours. The amount of cervical mucus varied, but was usually moderately profuse. The viscosity was extremely or moderately thin except in 2 patients.

TABLE 2

Post-coital analysis

NO.	AMT. MUCUS	TYPE	HRS.	HPF	GRADE	TOTAL ABNORMAL	ABNORMAL NUCLEI	ACROSOMES	MISCELL.	REMARKS
351	3 plus	Mod.	12	12	II, III	0				
322	2 plus	Thick	12	12	0	0				Female, anovulatory
302	4 plus	Thin	1½	50	IV	0.6%	0.3	0.3		Female, P.I.D.
325	4 plus	Thin	15	3	II	18	3	7.5	7.5	
319	2 plus	Mod.	38	50	III	0.6	0	0.3	0.3	Male, hypothyroid
400	4 plus	Mod.	18	50	III	0.6	0.3		0.3	
398	4 plus	Mod.	3	50	IV	3.8	1	1.7	1.1	
276	1 plus	Mod.	14	12	II	2.0	0.3	1.3	0.4	
304	4 plus	Thick	16	50	0	1.0	1.0	0	0	Cervicitis
329	3 plus	Thin	24	12	II	8.5	1.5	3	4.0	
275	2 plus	Thin	24	50	IV	1.3	0.3	0.3	0.7	
307	4 plus	Thin	16	12	II, III	8.0	1.3	5.0	1.7	
332	3 plus	Thin	14	50	II, III	2.6	0.3	0.3	2.0	
324	3 plus	Thin	14	6	III	5.0	0	2.0	3.0	
377	3 plus	Thin	4	25	III	3.0	1.0	0.7	1.3	
279	2 plus	Mod.	5	6	0, I	14.3	8.3	2.0	4.0	



No. 325

Name Address

Vol. 5 Cc Dnst. 46.5 m. Motility Grade

1. Normal (70%+) 81 %
2. Abn. Nuclei (0-9%) 8 %
3. Acrosomal (0-14%) 7 %
4. Misc. (0-9%) 4 %
a. Unclass. 1 %
b Amorph %
c. AEK %
d. PEK %
e Body 2 %
f End Ring %
g Immature %
h Megalo. 1 %
i Pinhead %
j
k
TOTAL ABNORMAL 19 %

2 Hr. 80 % 3
3 Hr. 60 % 3
5 Hr. 20 % 2
Nuclear Variability MARKED
Viscosity Norm
Opacity ++
Color WHITE
Cyto Extr. %
Per HPF
W B C 5
Crystals
Other Cells Debris ++++

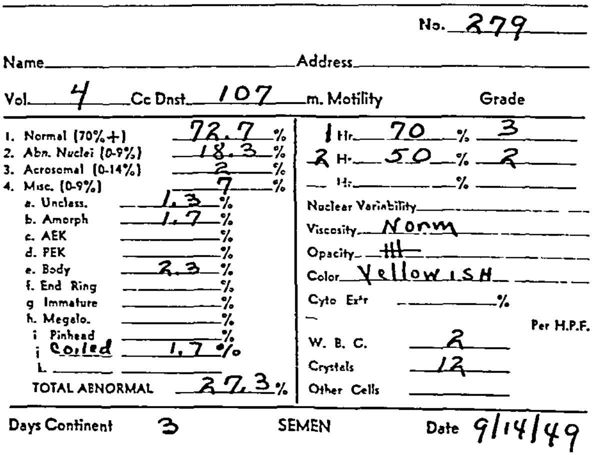
Days Continent 1 SEMEN Date 8/5/49

FIG. 3

In one of the latter, No. 322, the specimen was obtained during an an ovulatory cycle. The cervical mucus was scant and viscid, and the spermatozoa were immotile. In the second, No. 304, there was a marked cervicitis, associated with a profuse, viscid secretion containing numerous non-motile sperms. The number of spermatozoa obtained in the total group varied from 3 to 50 per high power field, a mode of 25 per high power field. The grade of motility varied from 0 to 4. Total abnormalities varied from 0 to 18 per cent, a mode of 2 per cent.

Tables 1 and 2 show a comparison in each of the 16 couples between semen analysis obtained by withdrawal or ejaculation and that observed post-coitus. In all except 1 patient, fewer total sperm abnormalities were found surviving in the cervical mucus than in specimens obtained from the male—only 2 per cent in post-coital specimens as contrasted with 17 per cent in semen obtained directly.

From the standpoint of morphology, sperm aspirated from cervical mucus (table 2) was far superior to that obtained from samples produced by withdrawal or friction (table 1). Case No. 329 graphically illustrates this point. In the semen analysis (fig. 2), a count of 70,000,000 sperm was made, of which 51 per cent were classified as abnormal. In the 24 hour Hühner test, there were only 8.5 per cent abnormal forms. A glance at tables 1 and 2 will show that this wide variation of abnormalities in semen analysis and post-coital analysis was quite uniform. In case No. 325, the exception, we found 18 per cent abnormal forms in the test performed 15 hours post-coitus as compared with the 19.3 per cent abnormalities in the semen analysis (fig. 3). This was the only exception to the finding of marked reduction of abnormal forms in surviving spermatozoa.



No. 279

Name Address

Vol. 4 Cc Dnst. 107 m. Motility Grade

1. Normal (70%+) 72.7 %
2. Abn. Nuclei (0-9%) 18.3 %
3. Acrosomal (0-14%) 2 %
4. Misc. (0-9%) 7 %
a. Unclass. 1.3 %
b. Amorph 1.7 %
c. AEK %
d. PEK %
e. Body 2.3 %
f. End Ring %
g Immature %
h. Megalo. %
i Pinhead %
j Coiled 1.7 %
k.
TOTAL ABNORMAL 27.3 %

1 Hr. 70 % 3
2 Hr. 50 % 2
Hr. %
Nuclear Variability
Viscosity Norm
Opacity +++
Color Yellowish
Cyto Ex'r %
Per H.P.F.
W. B. C. 2
Crystals 12
Other Cells

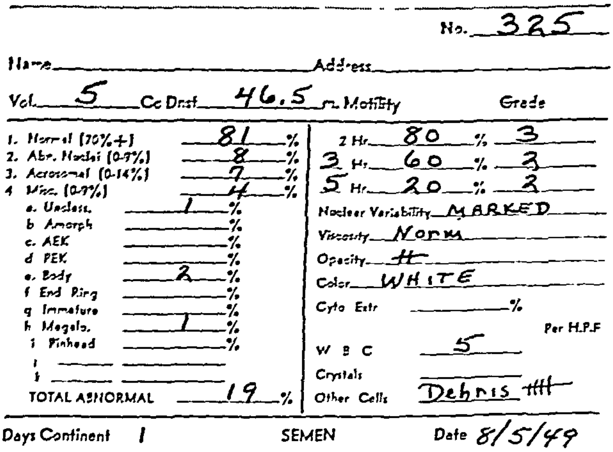
Days Continent 3 SEMEN Date 9/14/49

FIG. 4

DISCUSSION

The present study, although only a preliminary report, indicates that the endocervix acts as a storage depot for sperm which appear normal as judged by motility and morphology. Whether such spermatozoa remaining many hours after coitus are really normal, as demonstrated by their fertilizing ability, cannot be proved—at least by our present standards of analysis. Such spermatozoa remaining in cervical mucus at ovulation time appear of better quality inasmuch as they possess fewer abnormalities than the sperm examined in withdrawal

No.	[illegible]	TYPE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
251	3 plus	Mod.	12	12	II, III	0				
322	2 plus	Thick	12	12	0	0				Female, [illegible] [illegible]
302	4 plus	Thin	1½	50	IV	0.6%	0.3	0.3		Female, P.I
325	4 plus	Thin	15	3	II	15	3	7.5	7.5	
319	2 plus	Mod.	35	50	III	0.6	0	0.3	0.3	Male, [illegible] thyroid
400	4 plus	Mod.	18	50	III	0.6	0.3		0.3	
398	4 plus	Mod.	3	50	IV	3.8	1	1.7	1.1	
276	1 plus	Mod.	14	12	II	2.0	0.3	1.3	0.4	
304	4 plus	Thick	16	50	0	1.0	1.0	0	0	Cervicitis
320	3 plus	Thin	24	12	II	8.5	1.5	3	4.0	
275	2 plus	Thin	24	50	IV	1.3	0.3	0.3	0.7	
307	4 plus	Thin	16	12	II, III	8.0	1.3	5.0	1.7	
332	3 plus	Thin	14	50	II, III	2.6	0.3	0.3	2.0	
324	3 plus	Thin	14	6	III	5.0	0	2.0	3.0	
377	3 plus	Thin	4	25	III	3.0	1.0	0.7	1.3	
279	2 plus	Mod.	5	6	0, I	14.3	8.3	2.0	4.0	



No. 325

Name ______ Address ______

Vol. 5 Cc Dnst. 46.5 m. Motility Grade

1. Normal (70%+) 81 %
2. Abr. Nuclei (0-9%) 8 %
3. Acrosomal (0-14%) 7 %
4 Misc. (0-9%) 4 %
   a. Useless. 1 %
   b Amorph ______ %
   c. AEK ______ %
   d PEK ______ %
   e. Body 2 %
   f End Ring ______ %
   g Immature ______ %
   h Megalo. 1 %
   i Pinhead ______ %

TOTAL ABNORMAL 19 %

2 Hr. 80 % 3
3 Hr. 60 % 3
5 Hr. 20 % 2

Nuclear Variability MARKED

Viscosity Norm

Opacity ++

Color WHITE

Cyto Extr ______ %

Per H.P.F

W B C 5

Crystals ______

Other Cells Debris ++++

Days Continent 1

SEMEN

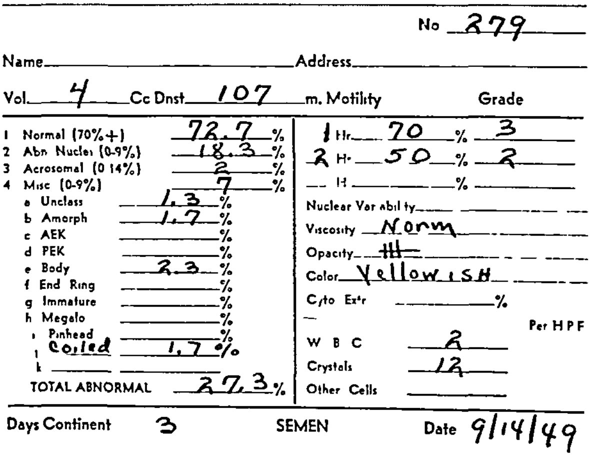
Date 8/5/49

FIG. 3

In one of the latter, No. 322, the specimen was obtained during an an ovulatory cycle. The cervical mucus was scant and viscid, and the spermatozoa were immotile. In the second, No. 304, there was a marked cervicitis, associated with a profuse, viscid secretion containing numerous non-motile sperms. The number of spermatozoa obtained in the total group varied from 3 to 50 per high power field, a mode of 25 per high power field. The grade of motility varied from 0 to 4. Total abnormalities varied from 0 to 18 per cent, a mode of 2 per cent.

Tables 1 and 2 show a comparison in each of the 16 couples between semen analysis obtained by withdrawal or ejaculation and that observed post-coitus. In all except 1 patient, fewer total sperm abnormalities were found surviving in the cervical mucus than in specimens obtained from the male—only 2 per cent in post-coital specimens as contrasted with 17 per cent in semen obtained directly.

From the standpoint of morphology, sperm aspirated from cervical mucus (table 2) was far superior to that obtained from samples produced by withdrawal or friction (table 1). Case No. 329 graphically illustrates this point. In the semen analysis (fig. 2), a count of 70,000,000 sperm was made, of which 51 per cent were classified as abnormal. In the 24 hour Hühner test, there were only 8.5 per cent abnormal forms. A glance at tables 1 and 2 will show that this wide variation of abnormalities in semen analysis and post-coital analysis was quite uniform. In case No. 325, the exception, we found 18 per cent abnormal forms in the test performed 15 hours post-coitus as compared with the 19.3 per cent abnormalities in the semen analysis (fig. 3). This was the only exception to the finding of marked reduction of abnormal forms in surviving spermatozoa.



No 279

Name ______ Address ______

Vol. 4 Cc Dnst 107 m. Motility Grade

1 Normal (70%+) 72.7 %
2 Abn Nuclei (0-9%) 18.3 %
3 Acrosomal (0 14%) 2 %
4 Misc (0-9%) 7 %
a Unclass 1.3 %
b Amorph 1.7 %
c AEK ____ %
d PEK ____ %
e Body 2.3 %
f End Ring ____ %
g Immature ____ %
h Megalo ____ %
i Pinhead ____ %
j Coiled 1.7 %
k ____
TOTAL ABNORMAL 27.3 %

1 Hr. 70 % 3
2 H. 50 % 2
__ H ____ %
Nuclear Variability ____
Viscosity Norm
Opacity +++
Color Yellowish
C/to Ex'r ____ %
Per H P F
W B C 2
Crystals 12
Other Cells ____

Days Continent 3 SEMEN Date 9/14/49

FIG. 4

DISCUSSION

The present study, although only a preliminary report, indicates that the endocervix acts as a storage depot for sperm which appear normal as judged by motility and morphology. Whether such spermatozoa remaining many hours after coitus are really normal, as demonstrated by their fertilizing ability, cannot be proved—at least by our present standards of analysis. Such spermatozoa remaining in cervical mucus at ovulation time appear of better quality inasmuch as they possess fewer abnormalities than the sperm examined in withdrawal samples. Perhaps the cervical mucus at ovulation time is selective in its action upon spermatozoa, by filtering out abnormal forms, thus permitting normal sperm egress into the uterus. If a large percentage of abnormal forms are so simply deleted by a natural process the question then arises as to how significant is the presence of abnormal nuclei, defective acrosomes, and body and neck deformities which are observed in the semen analysis. Williams attaches the greatest significance to spermatic abnormalities. In his report of 370 men investigated for sterility, 80 were found to have in excess of 40 per cent abnormal sperm. Only 3 of the wives in this entire group of 80 couples conceived; one of the 3 miscarried. It is his belief that where there is a large percentage of abnormalities obtained in semen, the normal appearing sperm are probably incapable of impregnation. Seymour reports an interesting observation concerning a donor specimen containing 94 million sperm per cubic centimeter, with good motility and only 3 per cent abnormal forms,—an apparently excellent specimen. This sample was used for insemination in 17 patients, none of whom conceived,—a *clinically sterile specimen. The fertility of this group of 17 patients was proved* when other samples were used for insemination.

Our observations suggest that the morphology of sperm surviving in cervical mucus is important in the evaluation of the sterile couple. Just how important remains to be proved by further study. However, at the present time, the morphological studies of post-coital specimens can serve as a check against the original semen analysis. For example, in case No. 279, a competent urologist had reported that the semen analysis was normal in every respect. Our morphological studies on cervical mucus obtained 5 hours post-coitus revealed 14.3 per cent total abnormal forms, with 8.3 per cent abnormal nuclei, a high percentage of abnormalities. We therefore requested a withdrawal sample for our own examination. This specimen revealed 27.5 per cent abnormal forms, chiefly sperm with abnormal nuclei (18.3 per cent). Figure 4 gives the semen analysis in detail.

In the opinion of the authors, a satisfactory post-coital test does not reveal the true percentage of abnormal sperm in the semen, inasmuch as apparently good post-coital samples may be found when the male partner has a highly abnormal semen. On the other hand, a satisfactory post-coital test does show that the cervical secretions are favorable to the longevity of sperm and that coitus was well timed, occurring at or near ovulation.

CONCLUSIONS

Motile spermatozoa recovered from cervical mucus from 1½ to 38 hours post-coitus appear normal when judged by the accepted standards for motility and morphology.

Stained smears of cervical mucus post-coitus, when compared to stained smears of semen direct from the male, show a remarkable reduction in the percentage of abnormal spermatozoa.

Note: Since the completion of this paper, we discovered that a similar survey had been made by Dr. Fred A. Simmons with similar results. He found that the percentage of normal sperm in cervical mucus was greater than that in the individual semen specimen.

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REFERENCES

Seymour, F. I.: J. A. M. A., **112:** 1817, 1939.
Simmons, F. A.: The Cervix Uteri in Infertile Matings. In: The Problem of Fertility, edited by E. T. Engle. Princeton University Press, 1946, p. 219.
Simmons, F. A.: Clinical Interpretation of Semen Analysis. In: Diagnosis of Sterility, edited by E. T. Engle. Springfield, Ill.: C. C. Thomas, 1946, p. 27.
Stein, I. F. and Cohen, M. R.: Sperm survival at estimated ovulation time: Prognostic significance. Fertility and Sterility, 1:169, 1950.
Williams, W. W.: J. Urol., **32:** 201, 1934.
Williams, W. W.: Trans. Am. Soc. for Study of Sterility, 1946, pp. 139-149.

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A NEW CHEMICAL APPROACH TO THE DISSOLUTION OF URINARY CALCULI

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It is an accepted fact that surgery or instrumental manipulation is the only sure means known at present for the removal of urinary calculi in the majority of patients with this discouraging and often recurrent disease. A nonoperative method of treatment is desirable, and has long been sought after.

An extensive review of the history of the many attempts at dissolution of urinary calculi has been given by Keyser.[1] Among the chemicals which have been tried are alkalies,[2] mercurochrome,[2] organic acids,[1, 3, 4, 5] sodium benzoate and glycine,[6] sodium hexametaphosphate,[3] several of the strong inorganic acids and oxydizing agents, such as aqua regia and permanganate,[1] inorganic salts as sodium chloride, sodium phosphate and magnesium phosphate,[4] solutions of enzymes,[1, 4] and finally citrate solutions.[3, 7] None of these approaches have been entirely successful. Scherer, Claffey, and Keyser[4] have claimed that solutions of enzymes, especially urease, in combination with citrates, have brought about rapid and complete disintegration of stones by an apparent change in their organic components. We have been unsuccessful in applying their results clinically.

More success has attended the application of reagents which withdraw calcium and bind it in a water-soluble form. These solutions (Suby's G and M) find clinical application in the treatment of soft calcium stones of the phosphate and carbonate variety. Unfortunately, stones of this category make up only a part of the total number of calculi encountered. The acid citrate solutions, even the improved formula M, have the further disadvantage of being irritating to tissues, apparently because of their low pH and hypertonicity. The principle involved in the action of citrate solutions on urinary calculi has been the most effective yet applied; we were therefore led to look for a solution whose action would also be based on this principle, but of wider applicability and more favorable physiological properties. This paper is a description of such a solution, of the methods used, and of the results obtained with it. The work was begun in 1947 and is still in progress at the J. Bentley Squier Urological Clinic of the Columbia-Presbyterian Medical Center and the Department of

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Read at annual meeting, American Urological Association, Washington, D C., May 31, 1950.

Dr. Gehres' manuscript was awarded a prize by the Committee on Scientific Research, Dr. Miley B. Wesson, chairman. *Editor.*

[1] Keyser, L. D.: J. Urol., **50:** 169, 1943.

[2] Crowell, cited by Keyser (loc. cit.).

[3] Albright, F., Sulkowitch, H. W. and Chute, R.: J.A.M.A., **113:** 2049, 1939.

[4] Scherer, P. C., Claffey, L. W. and Keyser, L. D.: Bull. Virginia Poly. Institute, vol. 38, No. 12, 1945.

[5] Flocks, R. H.: J. Iowa State Med. Soc., **35:** 321, 1945.

[6] Snapper, I., Bendien, W. M. and Polak, A.: Brit. J. Urol., **8:** 337, 1936.

[7] Suby, H. I., Suby, R. M. and Albright, F.: J. Urol., **48:** 549, 1942.

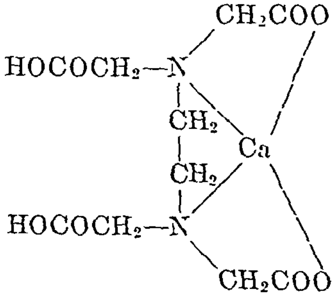
Bacteriology of the College of Physicians and Surgeons of Columbia University. The interest and support of Dr. Beatrice Seegal, executive officer of the Department of Bacteriology, and Dr. George F. Cahill, director of the Squier Urological Clinic, have been important in the progress of this work. This work was supported, in part, by a grant from the National Institute of Health.

THEORETICAL DISCUSSION

Urinary calculi are composed of both inorganic and organic constituents. The results of the few investigations[1] which have been made on the organic component indicate that it is colloidal in nature. As a result of our experimental observations we are convinced that this component is of little importance in the problem of stone dissolution.

The principal inorganic constituents of urinary stones are calcium, magnesium and ammonium cations in various combinations with the anions phosphate, carbonate, oxalate and urate. The actual mineral components present in stones cannot be determined from their elementary composition since these cations and anions exhibit many complex possibilities of combination. The physical and chemical properties of the stone depend primarily on the mineral species present rather than on the elementary composition.

We have chosen for study solutions of ethylenediamine tetra-acetic acid (calsol), which forms a soluble complex with calcium of the following structure:



Primarily because of the cage-like structure of carboxyl and amino groups which surrounds the calcium, the latter is effectively removed from the solution. Removal of calcium from the solution is so complete than even the most insoluble calcium oxalate dissolves readily in the calsol solution.

EXPERIMENTAL METHODS

Source of calsol: Ethylenediaminetetraacetic acid was first described in 1937 in a patent by the German firm of I. G. Farben for use in the dye industry. The material is commercially available from a number of sources. We have chosen the shorter descriptive term calsol to replace the unwieldy technical name of the compound.

Solution of Sodium Calsol

Calsol	100 gm.
Sodium hydroxide ..	40
Water to make	1 liter

Suspend the calsol in the water and add 36 gm. of the sodium hydroxide. Stir until all is dissolved and then add the remaining sodium hydroxide in small portions until the desired pH is reached. This results in a 10 per cent solution. The 7, 5, 3, and 1 per cent solutions were prepared by appropriate dilution of the stock 10 per cent solution.

In vitro testing. In devising methods for the in vitro testing of stone dissolving solutions we have been guided partly by the earlier experimental methods of Suby,[7] Albright,[3] and Scherer.[4] It must be recognized that calculi vary greatly in both chemical and physical make-up, so that rough data from a large number of stones are preferable to precise data on a small number in order to have an adequate basis for drawing valid statistical conclusions. The experimental methods used in the present work have been accurate yet simple enough to yield a significant number of observations.

The stones used in this work were obtained from the stone collection of the Squier Urological Clinic. For the comparison of a series of solutions, a group of stones were chosen all from the same patient and the same organ, i.e. kidney or bladder. This insured that the stones used in any given comparison series had closely similar compositions, but often limited the amount of experimental work possible.

The effect of the solutions on stones was measured by the loss in weight of the stone after exposure to the solution. The stones, which ranged in weight from 50 to 500 mg. each, were weighed on an analytical balance and immersed in 100 ml. of the solution. The stones were removed from the solution after 24 hours, gently blotted with filter paper and dried for 24 hours at 37 C in air. Care was taken to avoid breaking off small pieces of the stones which had been softened by action of the solution. In many cases the organic matter in the outer layer of the stone did not dissolve, but floated off into the solution. It was this observation that led us to conclude that the organic matter did not interfere with dissolution of the stone.

The data are recorded as per cent of the original weight which had gone into solution. The use of per cent weight loss as a measure of the effectiveness of a solvent in dissolving calculi permits the evaluation of a large mass of experimental data, but ignores one qualitative aspect of the solution process which would undoubtedly be important in clinical usage, the softening action of the solvent. Stones exposed to the action of our solutions undergo a change in physical structure which makes them softer, more friable, and more easily broken up in situ. This means that in the patient the stone may be eliminated more rapidly than the in vitro data indicate.

Table 1 shows that the experimental procedure of handling and drying the stones caused no significant change in weight, using tap water as a control.

Effect of concentration and pH. Stable solutions of calsol can be obtained at a pH of 4 or greater. A series of experiments showed that aside from stones which were so soluble that changing the pH had little effect, the optimum pH was between 7 and 8, the most desirable pH from the standpoint of clinical use. Solutions of pH less than 7 were definitely less effective, while a pH greater than 8 sometimes had an adverse effect. Although the dissolving power of the solution increases with concentrations, the effect is not great above 3 per cent. Since the 1–3 per cent solutions are close to isotonic, these concentrations were used in further work.

In vitro comparison of calsol and acid citrate solutions. Having established the optimum pH and concentration for the effective use of calsol solutions in vitro, these solutions were compared with solution G in the same manner. The original description of the citrate solutions pointed out that these solutions were effective only against the more soluble types of stones; this finding is borne out by our results. Table 2 shows that solution G had almost no effect against a series of oxalate stones. Calsol solutions, on the other hand, were quite effective in dissolving the same stones.

TABLE 1. *Effect of water on stones*

CASE NO.	% LOSS	CASE NO	% LOSS
4612	4	4313	1
3178	4	5121	0
3188	2	5144	1
5321	6	2735	2 (Gain)
5171	0		

TABLE 2. *Summary of in vitro comparisons of stone-dissolving solutions*

TYPE OF STONE	TOTAL NUMBER TESTED	NUMBER ATTACKED BY:		
		Solution G	1% Calsol	3% Calsol
Oxalate	8	0	7	8
Urate	16	4	12	14
Soft	22	13	16	21
Totals	46	17	35	43

Urate stones are slightly more susceptible than oxalate stones to acid citrate solution since 4 out of 16 showed an appreciable decrease in weight when treated with citrate. However, even in this series calsol proved to be superior to acid citrate, since calsol attacked 14 out of 16 stones, and in every case at a more rapid rate of solution.

All other calculi are grouped under the heading of soft. This category included the phosphate and carbonate variety and a single cystine stone. As is evident from the figures in table 2, acid citrate solution had greater dissolving action against this series of calculi than against the other series. But again it did not have as great an effect as the calsol solutions. Sixty-two per cent of the stones of this series were attacked by solution G to an appreciable degree, whereas 94 per cent were dissolved by calsol. In every case, even those where solution G did dissolve the stone to some extent, calsol was as good as or definitely better than solution G.

The in vivo effect of calsol solutions. A. Effect on normal tissues: To test the effect on bladder tissues an experiment was set up similar to that described by Suby, Suby and Albright.[7] Rabbits under intravenous nembutal anesthesia were catheterized with a No. 18 Foley catheter from which the inflatable bag had been removed. Through this double lumen catheter the bladder was continuously irrigated for 5 to 6 hours at the rate of 40–45 drops per minute. The outlet of the system was raised 10 cm. above the level of the abdomen to produce positive pressure, thus insuring adequate distention of the bladder. Following the period of irrigation, the rabbit was killed and autopsied. The bladder was examined grossly and sections taken for microscopic study. Photomicrographs of sections following irrigation are reproduced in figure 1. It will be noted that 1 and 3 per cent calsol had little or no effect on bladder epithelium.

B.Toxicity: The minimal lethal dose of calsol solutions was determined in 20 gm. mice. When administered in a single interperitoneal injection, 0.1 cc of 3 per cent or 0.5 cc of 1 per cent calsol caused death in 10 minutes. The same total amount of solution when given in 10 doses at 15 minute intervals produced no toxic effects. Mice receiving a total of 0.7 cc of 1 per cent calsol per day for 6 days showed no evidence of intoxication. At autopsy these animals demonstrated no gross pathological changes.

Calsol solutions, when administered by mouth, caused no apparent ill effects to rats or mice. A 1 per cent calsol solution was supplied to the animals as their only source of drinking water. Over a period of weeks the animals continued to gain weight and appeared normal in every respect. One rat and two mice each bore litters of normal offspring during this period.

The method used to prepare experimental animals with urinary stones was the direct introduction of human renal and vesical calculi into the bladders of rabbits through a suprapubic incision. With no further treatment these stones remained in place unchanged for periods of several months. This operation successfully placed stones in a location in the urinary tract easily accessible to experimental irrigation.

In the first series of 6 animals urate stones were implanted. It is well known that irrigation with acid citrate solution does not dissolve stones of this type. In vitro they are difficultly soluble even in calsol solutions. Nevertheless, in the series of 6 animals, irrigation with calsol completely dissolved 4 of these stones and completely disintegrated another, of which the fragments were found at autopsy in a urethral diverticulum. Only one stone was unaffected. These remarkable results were obtained on a treatment schedule of 1 liter in 5 hours at intervals of 2 to 10 days until a total of 1 to 5 liters used on each animal was attained.

Surprisingly, the next stones treated in rabbits were not completely dissolved although the stones in question were of the soft phosphate-carbonate type, which in vitro showed a high solubility. In our opinion, the results can only be attributed to mechanical factors which removed the stone from contact with the solution. For example, in rabbits Nos. 367 and 459, the stone, showing signs of partial dissolution, was found at autopsy in the urethra.

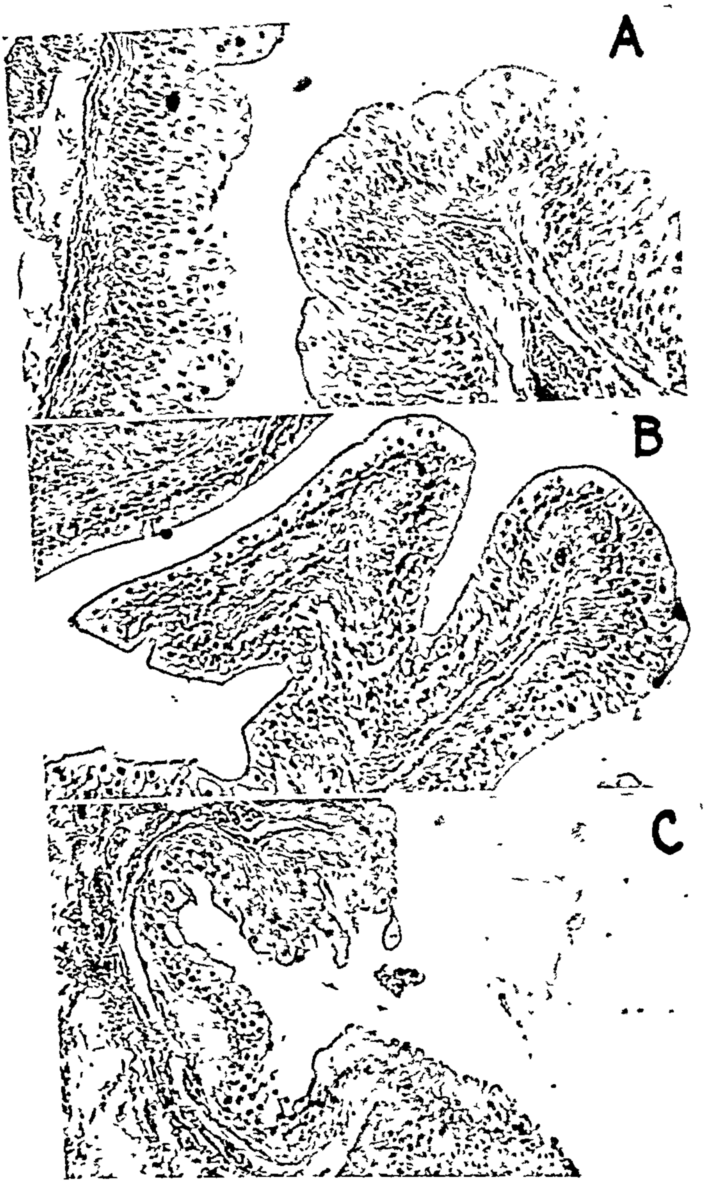


FIG. 1. *A*, section of rabbit's bladder after irrigation with 1 per cent Na calsol shows no inflammation of epithelium. *B*, section of rabbit's bladder after irrigation with 3 per cent Na calsol shows no inflammation of epithelium. *C*, section of rabbit's bladder after irrigation with 6 per cent Na calsol shows moderate inflammatory changes at unnecessarily high concentration.

CLINICAL RESULTS

The application of the laboratory results to clinical usage has been investigated.

Seven patients have been treated with calsol since completion of the animal experiments. The clinical data, however, must be regarded as no more than preliminary in nature. Table 3 summarizes the clinical work.

Since the first three patients were scheduled for surgical procedures (two had benign prostatic hypertrophy, and one a fibrous contracture of bladder neck), there was only a limited time available for treatment with calsol. The patients were carefully observed for possible toxic reactions to the solution.

TABLE 3. *Clinical results with calsol*

PATIENT	POSITION OF STONE	LENGTH OF IRRIGATION	DISSOLUTION	COMMENT
R. F. No. 942409	Bladder	Continuous 3 days	No	Tidal drainage not used; bladder not adequately filled; stone not properly bathed by solution.
D. E. No. 710491	Bladder	Continuous 36 hours.	No	Stone passed into patulous urethra; in little contact with solution.
E. Z. No. 926217	Bladder	Continuous 5 days	About 25% see x-ray	Toxic reaction; see comment in text
F. W. No. 713460	Kidney	Intermittent one month	No	Stone inaccessible; not bathed by solution; acid citrate also tried but not tolerated by patient.
A. H. No. 946441	Kidney	Intermittent one month	About 50% see x-ray	Acid citrate tried but not tolerated; further treatment with calsol planned.
W. P. No. 969624	Bladder	Continuous 24 hrs.	About 65%	Properly irrigated by tidal drainage; stone not opaque; dissolution determined cystoscopically.
J. C. No. 973667	Bladder	Intermittent 3 days	100% see x-ray	Properly irrigated by tidal drainage; complete dissolution determined by x-ray and cystoscopy.

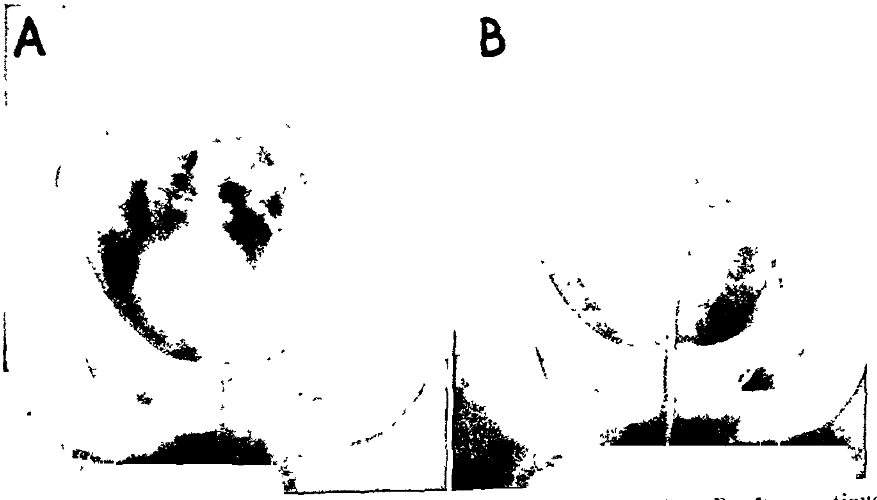


FIG. 2. Case E. Z., No. 926217. *A*, bladder stone prior to irrigation *B*, after continuous irrigation for 2 days with 1 per cent Li calsol.

The only toxic effect followed the inadvertent use of a lithium solution of high pH. The patient (E. Z.) had been on 1 per cent lithium calsol pH 7.3 for two days continuously with no complaints. Due to an error in preparing the solution, 1 per cent lithium calsol pH 9.0 was administered the three following

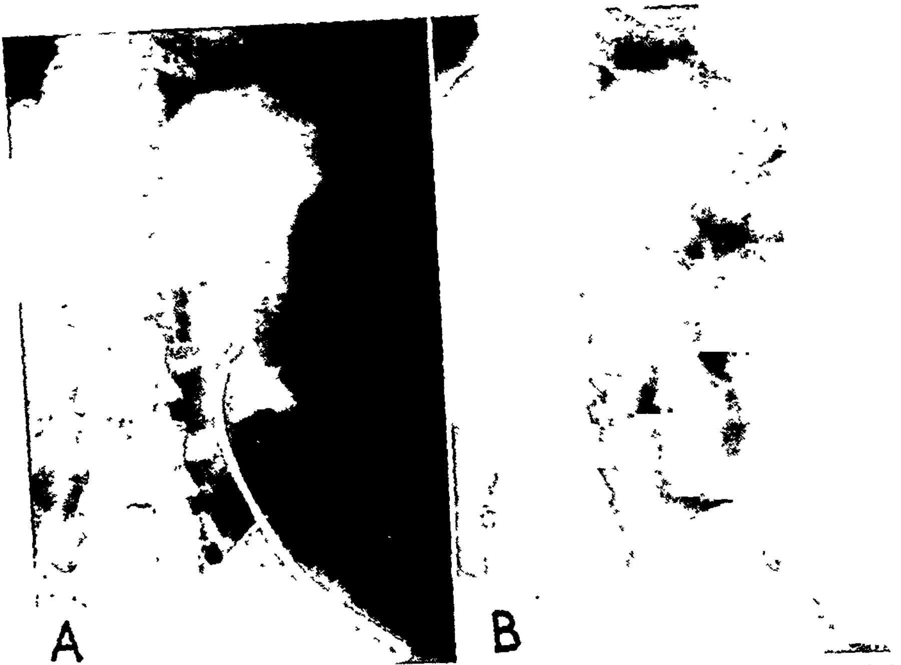


FIG. 3. Case A. H., No. 946441. *A*, left kidney stone prior to irrigation. *B*, after infrequent, intermittent irrigation for 1 month with 1.5 per cent Na calsol.

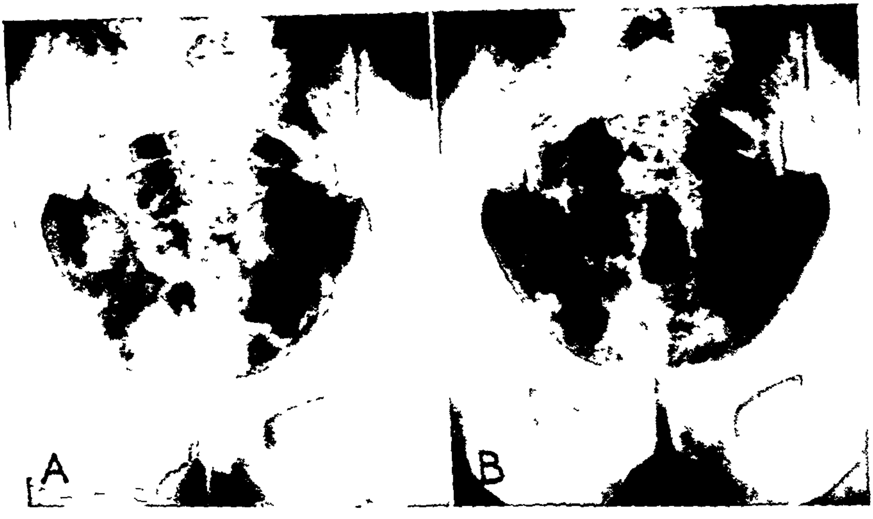


FIG. 4. Case J C., No. 973667. *A*. bladder stones prior to irrigation. *B*, after intermittent irrigation for 3 days with 1 5 per cent Na calsol.

days. At this time, signs and symptoms of acidosis developed. The patient returned to normal quickly following cessation of irrigation and institution of appropriate therapeutic measures. See figure 2.

During the short period of irrigation in the first 3 patients, little or no x-ray evidence of stone dissolution was seen except in the case of E.Z. The single large radio-opaque stone in this patient decreased one-fourth in diameter in a

2 day period. By cystoscopic observation during the course of the treatment and by direct observation during operation following cessation of treatment the bladder mucosa appeared normal in all 3 cases.

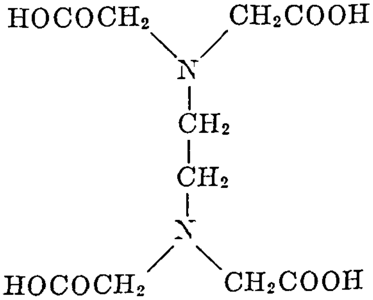
Good results were obtained in 3 of the next 4 cases, although considerable mechanical difficulty was encountered in irrigating the kidney of one due to blocking of ureterostomy tubes by mucus, and in adjusting the nephrostomy tubes in another so that the solution could bathe the stones. See figures 3 and 4. Following improvement of the irrigating technique, and with the use of a nearly neutral and isotonic sodium calsol solution, complete dissolution of hard, though poorly radio-opaque bladder calculi was accomplished without toxic effects in the last 2 cases. This was determined by cystoscopy in one and by both x-ray and cystoscopy in the other. In each the bladder appeared the same as it had prior to irrigation. The importance of insuring adequate contact between stone and solution is obvious, but cannot be overemphasized. In the early cases, this contact was lacking for one of two reasons: a) The stones were in an inaccessible position (e. g. in a deep calyx of the kidney or in the urethra); b) the irrigating tubes were located too near each other, resulting in insufficient circulation of the irrigating solution through the organ concerned.

The effects of (B) were finally eliminated in the bladder by partial filling of the organ as with a tidal drainage apparatus. In the kidney, proper adjustment of the irrigating tubes was of some help.

In future clinical work it is planned to discontinue use of lithium calsol solution because of the possible toxicity of the lithium ion and because the sodium solution was found to be equally effective in vitro and in vivo. A sodium calsol solution of 1.5 per cent concentration and pH 7.5 has been chosen for further work as it appears to be more nearly isotonic than the 1 and 3 per cent solutions previously used. This solution is being made up for us by Lederle Laboratories through the courtesy of Dr. J. H. Williams.

SUMMARY

A successful reagent for the dissolution of urinary calculi is described. Its action is based on the principle of binding calcium in a water-soluble form. This reagent is the sodium salt of ethylenediaminetetraacetic acid, calsol:



In vitro, this reagent has optimal dissolving effect on urinary calculi in solutions of 1 to 3 per cent and pH 7 to 8. The optimum concentration for clinical use appeared to be 1.5 per cent (isotonic).

Comparison with acid citrate G solution showed that of stones obtained from 46 separate patients, 17 were attacked by solution G, 35 by 1 per cent calsol, and 43 by 3 per cent calsol.

In vivo, normal rabbit bladders exposed to the solutions of calsol for 5 to 6 hours evidenced little or no toxic effects. Such solutions administered orally to rats or mice were well tolerated. The calsol was recovered from the feces but not from the urine. It follows from this that local irrigation is the only feasible method of application.

Four out of 6 artificially implanted urate calculi were rapidly dissolved from rabbit bladders in vivo by irrigation with calsol.

Treatment with calsol was effective in 4 out of 7 patients with urinary calculi in a preliminary clinical trial.

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PENICILLIUM INFECTION OF THE URINARY TRACT

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We are confronted on occasion with the diagnosis and treatment of disease conditions which are fortunately very rare but by reason of their rarity they may tax our resources in regard to specific therapy. Fungus infections in the genito-urinary tract present just such a problem. It is our purpose in this report to call attention to a rare instance of fungus infection. Before reporting this unusual example of infection of the urinary tract by a Penicillium mold, it is in order to review fungus infections in general.

Most fungi enter the body 1) through hair follicles, 2) through the nasal passages, 3) through abrasions and injuries, and 4) through the alimentary canal. The types of tissue reactions induced in man by these organisms are extremely variable. Some species remain quite superficial in their effects, whereas others produce deep lesions or involve almost any of the internal organs. Some display reactions which are primarily local; others, reactions which are primarily systemic. Among the more common tissue changes seen in such infections are congestion, edema, exudation, hyperplasia, necrosis, suppuration, and scar tissue formation. It should be stated also that most pathogenic fungi display rather marked pleomorphic changes when transferred from diseased tissue to artificial media.

The fungi which are pathogenic to man occupy a position which may be well termed a "no man's land" for both the mycologist and the medical practitioner. Even well trained mycologists have no real first-hand knowledge of fungi pathogenic to man for several reasons: 1) some 88,000 various types of fungi have been reported, not all of which are necessarily pathogenic; 2) because of the relative undeveloped status of mycology as a part of medical education, there is a trend in medical education toward more study of the role that fungi play in relation to man, but the average practitioner is usually perplexed when confronted with the diagnosis and treatment of diseases caused by such organisms. A lack of proper understanding of these fungi may also be attributed, in part, to the fact that the mycologist is not acquainted with the clinical and pathologic aspects of the diseases which they produce.

At the present time the classification of fungi is still in a state of flux and it appears that it will only be through the combined efforts and collaborative studies of the clinician, pathologist, taxonomist, serologist, biochemist, and epidemiologist that order can be established in the field of medical mycology. Since 1900 a great many papers have appeared but most of the work has been crystallized in the studies of Chute (1911), Thom (1930), Jacobson (1932), Dodge (1935), Emmons (1940), Swartz (1943), Lewis (1943), Conant (1945) and Wolfe and Wolfe (1947).

Of the 88.000 fungi described, those pathogenic to man are fortunately limited to some 30 species of organisms. The latter are for the most part so-called "imperfect fungi." A few are ascomycetes, which are closely related to the yeast and others are actinomycetes, whose systemic position in a classification of fungi is still a matter of dispute. A brief description of the more common ones is in order and for practicable purposes they are divided into two general groups; namely those fungi which are most commonly found in 1) superficial and 2) systemic mycotic infections.

Group 1, or superficial infections, include a) Trichophytons, b) Epidermophytons, c) Microsporums, and d) Monilia albicans. In this first group, all of the pathogenic species except the latter, namely Monilia albicans have a tendency to invade the keratinized layers of the skin and its modifications such as the hair, nails, etc. The dermatomycoses caused by these fungi are commonly known as ringworm, tinea, jock itch, barber's itch, athlete's foot, favus and kerion. Monilia albicans, on the other hand, is probably best known in its connection with thrush, a disease most frequently seen in the throat and mouth of children, but occasionally appearing in old and debilitated persons as an etiological agent in pulmonary moniliasis. It is frequently seen also in conditions of the mucous membrane of the female genitalia, particularly in the form of vaginitis. There are several cases on record of essentially the same type of infection being present in the female urinary bladder. Monilia is also frequently found as a secondary invader in pulmonary tuberculosis. It might be added also that the Epidermophytons, Trichophytons, Monilias and in addition the orgnanism identified as Sporotrichum schencki all seem to be able to produce skin lesions known as an "id reaction" in sensitized persons.

Group 2 are fungi which most commonly produce systemic mycotic infections, namely: a) Blastomyces, b) Sporotrichum schencki, c) Coccidioides immitis, d) Histoplasma capsulatum, e) Actinomyces, f) Aspergillus, and g) Cryptococcus neoformans. The Blastomyces, Cryptococcus and Torula histolyticus, a closely related organism, in addition to attacking the skin, seem also to have a predilection for involvement of the central nervous system with the resulting clinical picture of chronic meningitis. These organisms do not involve the genito-urinary system with any great frequency, but in those cases in which they have been found in the genito-urinary tract they were part of a disease disseminated throughout the body.

Coccidioides immitis causes a highly fatal disease, probably most frequently occurring in California, Arizona and Texas. The infection is commonly known as valley fever or coccidioidal granuloma. It may occur as a mild respiratory infection with pleurisy, fever, chills, night sweats and headache. In the course of 2 or 3 weeks, however, a papillomatous lesion of the skin appears on the arms, thighs or scalp. Occasionally there may be some joint involvement. X-ray examination reveals pulmonary nodules resembling tuberculosis. There is a type of disease, due to the same organism in which meningeal symptoms are pronounced and death in these cases is more rapid. In those cases which recover, there is a rather marked reaction to intradermal injection of killed cultures of the fungus. This organism is reported as having been found in the urinary tract in the form of focal abscesses in the kidney.

Sporotrichum schencki, first described in 1898, usually enters the body through some minor injury and produces an ulcerative lesion which fails to heal. Gradually subcutaneous abscesses develop and spread along the lymphatics until a vessel is eroded at some point from which there is hematogenous dissemination to almost any organ in the body. There is an outbreak of epidemic proportions on record occurring in South Africa among native miners. The finding of this organ in the genito-urinary tract is again seemingly a part of a systemic infection.

Some 30 years ago, Darling reported a disease among natives in Panama characterized by fever, chills, emaciation, anemia, splenomegaly, leukopenia, and ulcerative lesions of the mucous membranes. This lesion he attributed to Histoplasma capsulatum. The primary site in the body affected by this organism seems to be the reticulo-endothelial system and as such presents a somewhat different picture from the ordinary pathogenic fungi. It may be confined to any local organ and two cases of genital lesions in the male were reported recently by Curtis and Crawley.

The occurrence of aspergillosis and actinomycosis is frequent enough to make further comment unnecessary at this time, save to say that the finding of these organisms in the genito-urinary tract is usually a part of a systemic infection.

Our immediate interest in this paper concerns the occurrence of a Penicillium mold in man as a pathogen. Thom classifies Penicillium as a form genus or specific group for the reason that so few species are known to exhibit a perfect stage or constant growth characteristics. Penicillium is grouped sometimes by other authors under the form genus ascomycetes or hyphomycetes. There are some 200 species of this organism and in general it is known as a blue mold or a green mold and is universally present on decaying organic matter. The best known species is Penicillium notatum from which is obtained the antibiotic penicillin. The conidiophores have the appearance of tiny brooms with chains of conidio on the tips of the broom. There is a rare report of this fungus having been recovered from patients with erysipelas, from bronchial secretions in cases of bronchial asthma, from external otitis, and from infections of the feet, hair, nails and skin. Salisbury in 1868, and Chute in 1911, are quoted as having isolated a Penicillium from the bladder urine of man. Because of the apparent rarity of fungus infections in the genito-urinary tract, and especially infections with the Penicillium mold, we considered it of sufficient interest to report the following case which occurred on our service.

CASE REPORT

University of Virginia Hospital No. 216250, B. M. G., a 56 year old entomologist referred to the authors in August 1945. The pertinent history dated back to 1929 when he first noticed a little pain on occasions in the region of the right kidney. In February 1936, he sustained an injury to the right lumbar region in an automobile accident, and three days later noted a mild episode of hematuria of short duration. In January 1937, there was an episode of fever and hematuria of 3 weeks' duration. He was seen then by a urologist who performed cystoscopy and urological examinations. Pyelograms showed some definite irregularity and blunting in the calyces of the right kidney in which there was also some calcification. No acid fast organisms were found at that time. According to the phenolsulfonphthalein test, the function was quoted as "excellent." From 1937 to date, the patient gave a history of episodes of dull right flank pain coming on suddenly and sometimes lasting for several days. The pain was described as colicky in nature, usually beginning over the kidney region and radiating down the course of the ureter and always accompanied by mild fever and malaise. The onset of the attack was followed in a few hours by the passage of balls of pink material in the voided urine. Following this there was a remission of the fever and no further symptoms until the occurrence of another attack some months later. The attacks were somewhat seasonable as the patient thought them more frequent in the fall and winter.

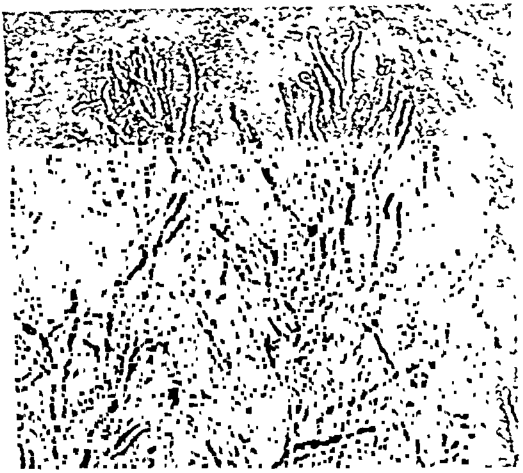

FIG. 1. Photomicrograph of an unstained smear of the fungus, Penicillium citrinum This was obtained from a readily growing culture on Sabouraud's media. Pure cultures of the fungus were obtained on many occasions from the urine of the reported case. They show the branching mycelium and through the microscope the conidia are easily visible on the tips of the brooms.

Physical examination revealed few findings of note with exception of hypertension (blood pressure 170/115). The eye grounds showed definite evidence of arteriosclerosis. X-rays of the chest were normal. Voided centrifuged urine showed 8 to 10 white blood cells per high power field with occasional clumps of white blood cells. Cultures from the bladder urine were sterile. Several subsequent studies were negative for tuberculosis. This patient was first seen immediately after one of his characteristic attacks, and a bolus of the pink material in the urine was identified as a large mass of mycelium. In the intervals between attacks mycelium was usually, but not always, identified in the voided urine. The fungus grew readily on Sabouraud's media in almost pure culture (fig. 1). Cultures from the kidneys obtained by ureteral catheterization revealed the mold to be present only in the urine from the right side. Pure cultures of the mold were kindly identified for us as Penicillium citrinum by the Northern Regional Research Laboratory of the U. S. Department of Agriculture.

COMMENT

A number of studies were made in an effort to determine the sensitivity of bacteria to this fungus or whether it produced antibiotic substances. The U. S. Department of Agriculture reported that it could be expected to produce a small amount of citrinum. We found that the latter had no apparent effect on the growth in vitro of cultures of staphylococci, streptococci or bacteria of the common coli series. We were not able to find any evidence of penicillin produced in the urine because when penicillinase was added to the cultures there was no evidence of penicillin being present. It is possible, however, that an antibiotic was being produced in vivo in this case because of the constant absence of pyogenic and other organism in the urine as evidenced by sterile urine cultures. In an effort to find some therapeutic agent with which to eradicate the infection further studies were made in the laboratory. These determinations showed that thymol, potassium iodide, methylene blue and other substances had no effect on the growth of the mycelium.* Tests for sensitivity of the mycelium in vitro to the various chemotherapeutic and antibiotic agents including sulfadiazine, penicillin, and streptomycin revealed that the organism was not inhibited in growth by any of these even in high concentration. Other than the three to five febrile attacks, lasting several days each year, there was little clinical evidence that the infection by this fungus was particularly harmful to this patient. No evidence of fungus infection according to careful medical survey existed elsewhere in the body. We did not feel justified in removing this kidney because of the presence of hypertension and arteriosclerosis. Even in the absence of any known therapeutic agent we felt that the probability of systemic infection was remote because the infection had been limited to the urinary tract since 1937.

The authors greatly appreciate the laboratory investigations that were carried out by Dr. O. B. Bobbitt of the clinical laboratory of the University of Virginia Hospital.

SUMMARY

A case of a rare infection of the urinary tract with a mold identified as Penicillium citrinum has been presented.

Penicillium citrinum is one of the 200-odd species of Penicillium of which Penicillium notatum is the best known because of its production of an active antibiotic commonly referred to as penicillin.

The symptoms simulated those found in renal colic in which there were periods of temporary obstruction to the right kidney for several hours followed by the passage of boluses of mold growth in the voided urine.

Other than these periodic febrile attacks, and momentary blockage of the right kidney, there was little evidence that profound damage had occurred from this unusual infection over the past twelve years. There was only moderate reduction in renal function, and the pyelographic evidence of pyelonephritis in the affected kidney was not marked.

This particular Penicillium produced little if any antibiotic substances on culture. It possibly produced a weak antibiotic in vivo as the urinary tract had remained sterile.

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* Cultures grew readily in dilutions of potassium iodide above 1/50 and thymol 1/100.

Up to the present time no chemotherapeutic agent has been found to which this fungus will respond.

Addendum: The patient died elsewhere, and cultures taken at autopsy showed Penicillium in the bladder and right kidney.

REFERENCES

CHUTE, A. L.: Penicillium glaucum in bladder. Boston Med. & Surg. J., **144**: 420, 1911.
CONANT, MARTIN, SMITH, BAKER AND CALLAWAY: Manual of Medical Mycology, 1945.
DODGE, C. W.: Medical Mycology, 1935.
EMMONS, C. W.: Yeasts, Molds and Actinomyces, 1940.
JACOBSON, H. P.: Fungous Diseases, A Clinico-Pathological Test, 1932.
LEWIS, G. M.: Introduction to Medical Mycology, 1943.
SALISBURY, J. H.: Am. J. Med. Sc., **55**: 4372, 1868.
SWARTZ, J. H.: Elements of Medical Mycology, 1943.
THOM, CHARLES: The Penicillia, 1930.
WOLFE AND WOLFE: The Fungi, 1947.

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A NEW OPERATING TABLE FOR PERINEAL PROSTATIC SURGERY

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One of the main reasons why surgeons do not perform perineal prostatectomies is because they do not have an operating table which places the patient in the correct position for adequate dissection of the perineal tissues. A faulty position makes anatomical exposure of the structures of the perineum difficult and often leads to injury of the nerves to the external and internal sphincters of the bladder or to a laceration of the rectum. Halsted devised a board with vertical uprights to hold the legs in position, supplemented with a sand bag beneath the sacrum to give flexion to the lumbar region. This gave a satisfactory position but necessitated lifting each patient into position and was not adaptable to different-sized patients. Young presented before the American Urological Association in 1920 a universal urological table for cystoscopy, x-rays and for surgical procedures. Such a table has been in constant use for 29 years in our operating suite. It is no longer made. Bidgood developed a mechanical device to fit on top of an ordinary operating table for perineal surgery. This apparatus, also, is no longer obtainable. A satisfactory operating table adaptable for all-sized patients is not manufactured at the present time. Since a number of good cystoscopic tables are available it is not necessary that a perineal prostatic surgical table be equipped with cystoscopic attachments. The main purpose is an operating table which will give adequate perineal exposure and be adaptable to all patients. It is our ambition to produce such a table in order to stimulate urological surgeons to perform perineal surgery. Many of the ideas of Young have been incorporated into the new table (figs. 1, 2 and 3). In general, the table here described has a flat top with moving central portion and perineal elevator. All the cogs are beneath the table top so that they do not interfere with the table pads and sheets in moving the patient into position and are shielded from being drenched with solutions in preparation of the patient for surgery. The table is sturdy and will not only accept a heavy patient in the correct position for perineal surgery but will maintain this position throughout the operative procedure. There is no lifting of the patient once the patient is placed on the table. A nurse can position the patient, thus doing away with orderly service. If the position is not adequate it can be changed at any time during the operation without interfering with the drapes or breaking of aseptic technique. It is adequate for female gynecological surgical procedures as female leg holders can be inserted in the place of the upright posts. It is also well adapted for combined abdominal and perineal surgical operations, because any desired position of the patient can be obtained for satisfaction of the surgeon. The table lends itself to abdominal, bladder, prostate and ureteral operations.

Table exhibited at annual meeting, American Urological Association, Washington, D. C., May 29–June 1, 1950.

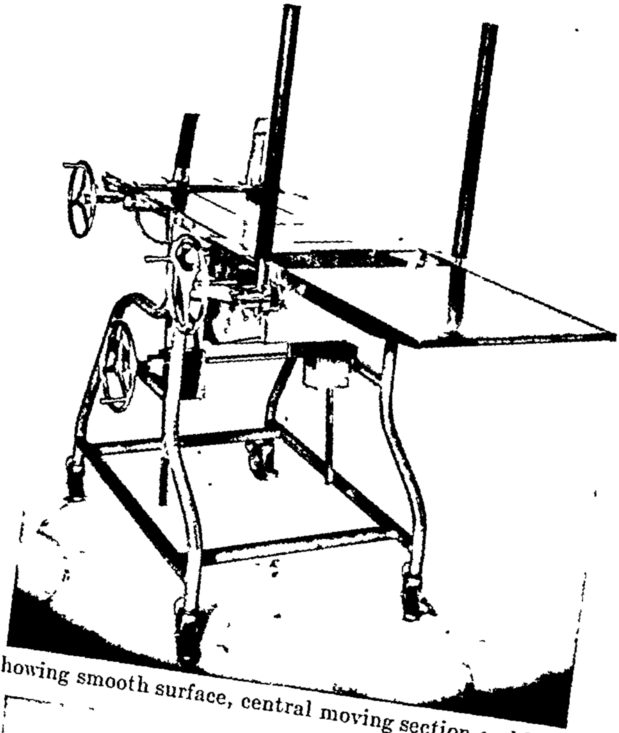

FIG. 1. Table showing smooth surface, central moving section and high shoulder braces

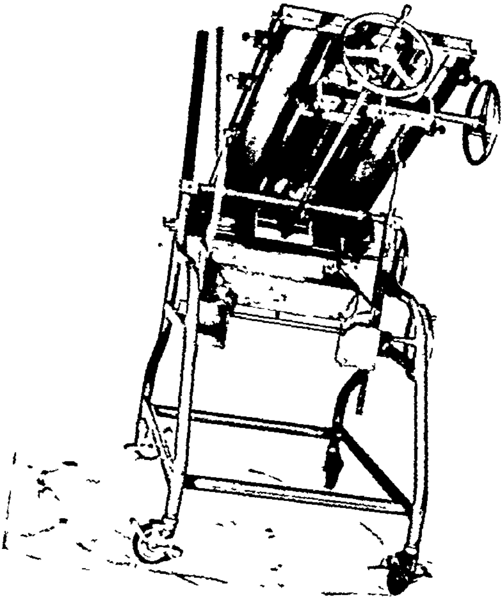

FIG. 2. View from the head disclosing gears beneath the table

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A NEW OPERATING TABLE FOR PERINEAL PROSTATIC SURGERY

CLYDE L. DEMING

From the Department of Surgery, Section on Urology, Yale University School of Medicine, and the Grace-New Haven Community Hospital, New Haven, Conn.

One of the main reasons why surgeons do not perform perineal prostatectomies is because they do not have an operating table which places the patient in the correct position for adequate dissection of the perineal tissues. A faulty position makes anatomical exposure of the structures of the perineum difficult and often leads to injury of the nerves to the external and internal sphincters of the bladder or to a laceration of the rectum. Halsted devised a board with vertical uprights to hold the legs in position, supplemented with a sand bag beneath the sacrum to give flexion to the lumbar region. This gave a satisfactory position but necessitated lifting each patient into position and was not adaptable to different-sized patients. Young presented before the American Urological Association in 1920 a universal urological table for cystoscopy, x-rays and for surgical procedures. Such a table has been in constant use for 29 years in our operating suite. It is no longer made. Bidgood developed a mechanical device to fit on top of an ordinary operating table for perineal surgery. This apparatus, also, is no longer obtainable. A satisfactory operating table adaptable for all-sized patients is not manufactured at the present time. Since a number of good cystoscopic tables are available it is not necessary that a perineal prostatic surgical table be equipped with cystoscopic attachments. The main purpose is an operating table which will give adequate perineal exposure and be adaptable to all patients. It is our ambition to produce such a table in order to stimulate urological surgeons to perform perineal surgery. Many of the ideas of Young have been incorporated into the new table (figs. 1, 2 and 3). In general, the table here described has a flat top with moving central portion and perineal elevator. All the cogs are beneath the table top so that they do not interfere with the table pads and sheets in moving the patient into position and are shielded from being drenched with solutions in preparation of the patient for surgery. The table is sturdy and will not only accept a heavy patient in the correct position for perineal surgery but will maintain this position throughout the operative procedure. There is no lifting of the patient once the patient is placed on the table. A nurse can position the patient, thus doing away with orderly service. If the position is not adequate it can be changed at any time during the operation without interfering with the drapes or breaking of aseptic technique. It is adequate for female gynecological surgical procedures as female leg holders can be inserted in the place of the upright posts. It is also well adapted for combined abdominal and perineal surgical operations, because any desired position of the patient can be obtained for satisfaction of the surgeon. The table lends itself to abdominal, bladder, prostate and ureteral operations.

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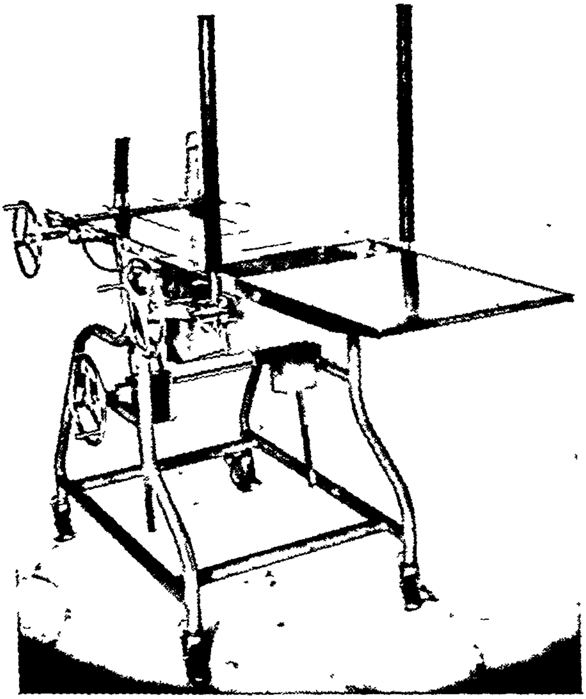

FIG. 1. Table showing smooth surface, central moving section and high shoulder braces

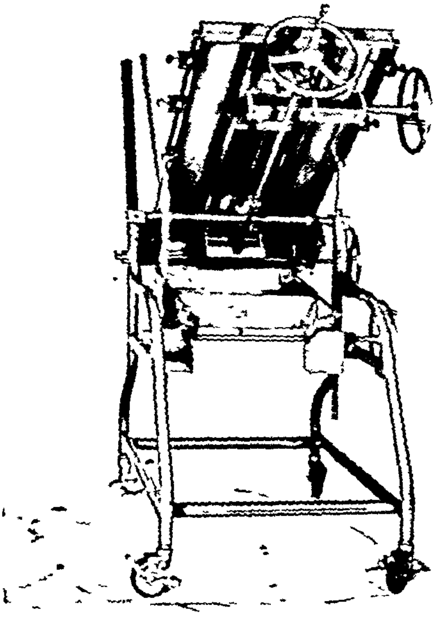

FIG 2. View from the head disclosing gears beneath the table

SPECIFICATIONS

The base is aircraft tubing mounted on four ball-bearing, swivel casters 4 inches in diameter with neoprene tires, individual foot locks of more than adequate capacity for free and easy rolling of the table.

The top is made of stainless steel plate in three sections. The center section consists of a perineal elevator at the foot of the table; the remaining part of the center section is affixed to the rear of the elevator so that it moves toward the foot of the table as the elevator is raised. The elevator is actuated by means of the wheel at the head of the table through a worm and worm gear. The shoulder supports may be adjusted to the individual patient by means of the rear side wheel, and the whole shoulder support moves forward with the center section of the table top when the elevator is raised. The table is tilted either forward or backward by the lower side wheel through a worm gear and rack drive. The leg supports may be set in any desired position and clamped against serrated washers for permanent holding power. After positioning, these leg irons may be flexed together by means of the front side wheel which drives two worms through two pairs of bevel gears. All the motions of the table are designed with adequate mechanical advantage so that they may be operated readily and easily when under load.

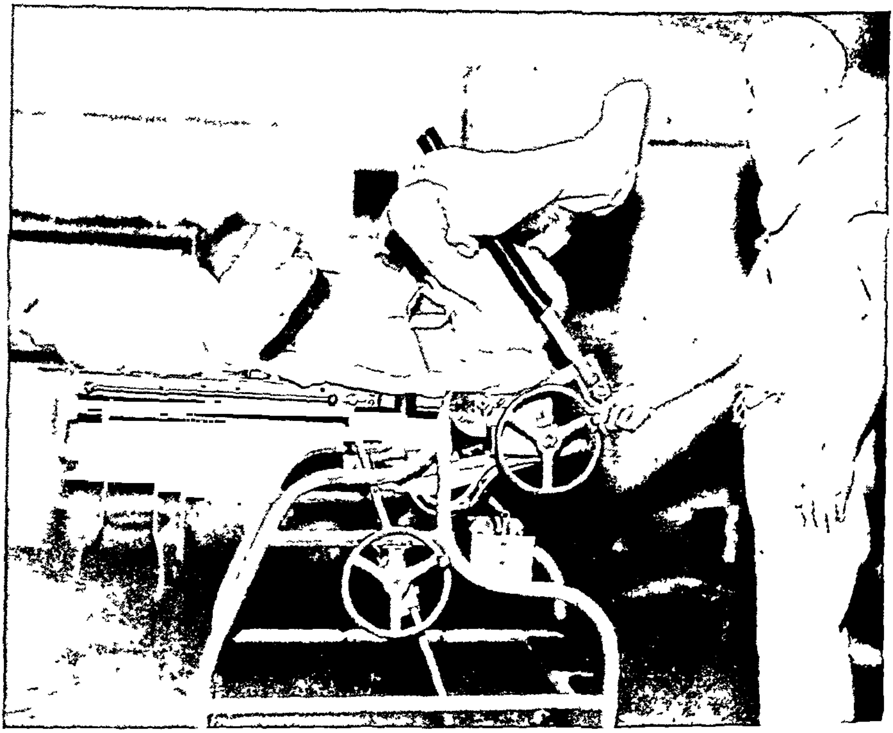

FIG 3 Patient being positioned to adjust the perineum at correct angle for exposure of the prostate.

The table extension for the feet locks into position and can not move against forward or downward pressure but can be removed easily by lifting and sliding it out.

All exposed surfaces are polished chrome plate and the drainage tray is made of stainless steel. The surfaces of all parts are easily cleaned and the gears are well protected against solutions. The table is designed with simplicity and ease of maintenance as the primary requirements.

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REFERENCES

Davis, D. M. and Warren, S. L.: New combined table for cystoscopy, roentgenography and fluoroscopy. J. Urol., **22:** 339, 1929.

Young, H. H.: An improved operating table, for general surgery, providing new features for urologic and gynaecologic work. Ann. Surg., **81:** 566, 1925.

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THE PHENOLSULFONPHTHALEIN TEST VERSUS THE CATHETER

JOHN K. ORMOND

From the Henry Ford Hospital, Detroit, Mich.

What I am presenting may be common property and nothing new, but I have never seen it in print and it has been new to various men who have worked with me.

I feel confident that every urologist has had the experience of catheterizing a patient whose urine is clear, finding an appreciable amount of residual urine and inciting an annoying cystitis or causing a chill. It is an unusual occurrence, but it can be very disconcerting when it does occur, and it makes one a bit hesitant about using the catheter in the presence of uninfected urine. Moreover, some patients find any instrumentation very unpleasant.

We are quite frequently consulted by elderly men complaining of nocturnal frequency, whose urine is clear and shows no abnormality except possibly a low specific gravity, and whose prostate may or may not show some enlargement on rectal examination. Often these men are planning to leave the city immediately for a long visit or for the winter, or may be passing through the city, and come for an examination. In these cases it may be important to know whether or not there is residual urine. In such cases we find the phenolsulfonphthalein test a very satisfactory substitute for the catheter. If the test is to be of any value it is important that before injecting the dye the patient empty his bladder insofar as he is able.

The dye is given intravenously and at the end of an hour the urine is collected and measured and the amount of dye excreted is read. Readings may be as high as 65 to 70 per cent in 1 hour. It is apparent that if the 1 hour reading is 65 per cent, there can be no appreciable residual, no matter what the amount of urine voided.

We consider 60 per cent as the average normal reading for the 1 hour test, and it is in those cases in which the reading falls below 60 per cent that the amount of urine voided is important. For example, if the amount voided is 150 cc and the phenolsulfonphthalein reading is 50 per cent, it is obvious that if there were 150 cc residual urine the phenolsulfonphthalein output would be 100 per cent, which is impossible. If there were residual of 100 cc the corrected reading would be 85 per cent, which is extremely unlikely; if the residual were 50 cc, the corrected reading would be 67 per cent. So we can conclude that there cannot be more than an ounce or so of residual. Since our policy has been to minimize the importance of residuals up to 100 cc, unless the symptoms are troublesome enough to cause the patient to desire operation, we would feel justified in the instance cited in refraining from catheterization and sending the patient on his trip reassured.

More frequently the amount voided is between 60 and 100 cc and in such cases the reasoning is even more clear. If the amount is 60 cc and the reading 40 per cent it is improbable that there is more than 30 cc residual. If the amount were 100 cc and the reading 25 per cent, it is evident that there could be over 100 cc residual, so catheterization is indicated. This may be expressed in a formula. Taking 60 per cent as the average normal 1 hour excretion of the dye, and letting P represent the actual one hour excretion in per cents, and U represent the amount of urine voided at the end of 1 hour, in cubic centimeters, the approximate maximum possible residual would be

$$\frac{60 - P}{P} \times U.$$

Of course in any one instance a low phenolsulfonphthalein output may be due to lowered renal function and not to residual urine.

ERRATA

Fig. 1, p. 366, March issue, belongs on p. 382

Fig. 1, p. 382, March issue, belongs on p. 366

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EXPERIMENTAL STUDIES ON THE MALE REPRODUCTIVE SYSTEM

CARL R. MOORE

From the Hull Zoölogical Laboratory, the University of Chicago, Chicago, Ill.

To have been selected to receive the 1950 award of the American Urological Association can only be regarded as a distinct honor. For this, and for being admitted into the fraternity of distinguished former recipients, I am most grateful. I like to consider such an action on the part of the Association as a recognition of the mutual values to each other of laboratory investigations and clinical studies, rather than merely a recognition of some personal merit. I hope also that your Committee's action in recommending the 1950 award is not subject to reversal. Your recognition that my experimental studies have not always followed a direct and logical course through a well organized, preconceived plan, always leading to clear cut solution of problems, may lead you to question the justification for making an award for accidents, good luck, blunderings and failures. A great deal of research is attended by just such factors, and luck may be good or bad depending upon one's point of view.

It has seemed appropriate for this occasion to present some of the highlights of personal experiences in research on the male reproductive tract that are now spread over a period of 34 years. And since honesty is a good basic policy it should be admitted at the outset that I did not map out logically, visualize, and organize a long-time investigation of the male reproductive tract; stumbling random procedures have largely dictated the course.

THE FREEMARTIN THEORY

In 1916, my celebrated predecessor, Professor Frank R. Lillie, was just announcing his observations and deductions from his studies on the freemartin. This animal is a genetic female individual of the bovine species, developed in

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Work reported here has been aided by the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

Read at the annual meeting, American Urological Association, Washington, D. C., May 29, 1950.

Note by editor. Dr. Moore was the recipient of the fourth annual award by the American Urological Association for research in the human male reproductive tract. The following citation was read by Dr. Thomas D. Moore, a member of the awards committee, in the absence of the chairman, Dr. Reed M. Nesbit:

"The Association is honored this year in making its Annual Award for Research on the Male Reproductive Tract to a man who has contributed greatly to our knowledge of the physiology of the testis and the influence of hormones upon the embryological development of this organ. In the pursuit of the latter studies, he developed new and ingenious techniques of investigation.

"Dr. Moore is best known to urologists for his researches which elucidated the thermoregulatory function of the scrotum. The immortal John Hunter made the observation that the undescended testis suffers a lack of development. Carl Moore found the reason why this maladjustment in testicular development occurs in the cryptorchid. His experiments were elegant, imaginative and conclusive; they provided a rational basis for the performance of orchidopexy.

"It is my privilege to present Professor Carl R. Moore, of the University of Chicago to receive this award, which symbolizes our approbation for the outstanding work that he has done."

utero as a twin to a male fetus. Because of the conditions under which it develops, it is subject to a reversal of its original female determination and actually develops more like a male than a female. In adult life this apparent female is incapable of reproduction and anatomically may show well formed testes, epididymides, and seminal vesicles instead of ovaries, oviducts and uterus. Although this strange creature has been known for two centuries, the conditions of its origin were not understood and the causative influences were wholly unappreciated.

Lillie found in his studies[1, 2] that the two sets of embryonic membranes (chorion and allantois) became fused during the development of twin fetuses in the cow, and extra-embryonic blood vessels from the two fetuses became so thoroughly connected that injection masses introduced into the umbilical artery of one fetus passed readily into the other. It was pointed out clearly that such an intermixture of bloods from two fetuses of the same sex caused no modifications, nor did the male partner of a heterosexual twin pair depart from normal; only the female of the heterosexual pair was modified. The explanation for this unusual set of circumstances introduced the concept that embryonic sex hormones play an important role during embryonic development. According to the theory, hormones secreted by testes passed into the female partner through the fused blood vessels and stimulated development of the male components of the female fetus; at the same time male hormone inhibited development of the female components. Thus the cortex of the ovary was prevented from developing and the medulla, or primary sex cord portion, became a testis; female ducts were inhibited and degenerated while the male ducts in the female, which normally undergo atrophy and disappear, were stimulated to produce the male tract. The ovary did not have a chance to secrete female hormones, hence the male partner continued to develop normally.

This theory of the freemartin condition constituted not only a beautifully logical and convincing explanation of the particular conditions found in heterosexual twins in cattle, and occasionally in pigs, but at the same time the hypothesis provided the basis for an explanation of the normal causal influences in the differentiation of sex during normal development in the vertebrates. Despite the apparent conclusiveness of the theory, Lillie insisted that the basic theoretical implications of the conception required experimental proof, and he mildly suggested that I attempt to produce a freemartin condition in laboratory animals by experimental procedures. This I started to do 34 years ago, and have made repeated attempts to penetrate the problem, but up to the present time I have failed utterly to accomplish the task undertaken. My publications during the course of investigations have been essentially by-products of my failures to do what I once regarded a simple task.

TESTIS TRANSPLANTATION

My first attempt to produce a freemartin condition in laboratory animals was the transplantation of testes into female rats or guinea pigs. The basic condition

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[1] Lillie, F. R.: The theory of the free-martin. Science, 43: 611–613, 1916.

[2] Lillie, F. R.: The free-martin: a study of the action of sex hormones in the fetal life of cattle. J. Exp. Zool., 23: 371–452, 1917.

to be realized appeared to be the introduction of male hormone into a developing female fetus at a time when the duct system and developing ovary were capable of being modified. Prior to 1927, we had no effective male hormone preparations available and therefore depended upon living tissues to secrete these substances. If testes were transplanted into young females perhaps male hormone would be secreted, and when such females were mated, their developing embryos might come under the influence of circulating male hormones and experience modification of the developing reproductive system. Some question existed whether sex hormones could pass the placenta, consequently testis tissue was transplanted in some cases onto the fetal membranes through an aperture in the pregnant uterus. None of these attempts resulted in any modification of developing young, but the results did introduce many unsolved problems on reactions of testis tissue after transplantation that were engrossing for a few years.

As a historical orientation, perhaps we should recall and characterize the years from about 1917 until 1926. It was a period in which prominence was given to testis transplantation in man as a method of rejuvenation. Popularly written, paper covered, pocket sized editions were available to extoll the merits of the Steinach rejuvenation method of warding off senility. Voronoff proposed that a national subsidy to permit him to transplant testes wholesale into sheep, in order to increase the growth of wool, would very soon yield income that would permit of retirement of the National French war debt. Physicians' offices were adorned with chrome-plated diathermy machines with which to treat gonorrheal epididymitis by heat waves generated in passing currents through the testis and epididymal tissues. The daily press carried accounts of taxi-drivers being waylaid and robbed of their testicles, presumably a black market opera tion to provide ultimately against aging millionaires attaining senility. The search for sources of living testis tissue for transplantation into man shifted to the chimpanzee, as claims were made that testes from this animal became incorporated in man and exercised untold effects.

Our experiments with transplantation of testis tissue yielded results contrary to the then current opinions.[3] Steinach described and illustrated testis grafts as consisting of degenerated seminiferous tubules and great hypertrophy of interstitial cells, thus producing his so-called "puberty gland." We obtained only an occasional testis graft fitting into this category of responses, and most of our recovered grafts showed active spermatogenetic cell divisions but no cases in which the final stage of spermatozoon differentiation occurred. Since effects alleged to be due to hormone secretions from the graft were seldom or ever seen in my experiments, the failure was presumably due to lack of "compensatory hypertrophy" of the interstitial tissue; consequently attention was directed toward obtaining this desired type of graft. The literature suggested two possible means whereby this might be accomplished. Undescended testes of the pig always revealed an unusual development of interstitial cells and it was thought possible that replacing a testicle into the abdomen, after descent, might in some manner induce such development. Thus experimental cryptorchidism was undertaken on guinea pigs. In the second case, it had been alleged that closure of the excurrent passageways from the testicle would cause seminiferous tubules to undergo degeneration that was followed by a compensatory development of interstitial tissue. Decrepit old male rats, according to Steinach, that were favored by a ligation of their vas deferens soon became so rejuvenated that they could easily overcome any virile young male in the colony, and would once again indulge in copulations.[4] With the desire to extend such marvelous new powers to ailing man, the operation called "vasoligation" or "vasectomy" was performed on a few men with alleged outstandingly good results.[5] Some American surgeons, always on the look-out for the most recent European developments, were interested, and early in the decade of 1920, one person in the East reported more than one hundred cases of vasoligation with the attendant glowing description of clinical results.

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[3] Moore, C. R.: Testis-graft reactions in different environments (rat). Am. J. Anat., 37: 351–416, 1926.

EXPERIMENTAL CRYPTORCHIDISM: VASOLIGATION: TEMPERATURE EFFECTS; SCROTAL FUNCTION

Our experiences with studies of experimental cryptorchidism on guinea pigs soon demonstrated that elevation of the adult testis through the open inguinal canal, and its confinement in the abdomen, led to complete dissolution of the spermatogenetic cells.[6] Degeneration, the casting off of loose cells into the tubular lumen, vacuolation of cells, giant cell formation, combined to remove essentially all cells of the seminiferous tubules with the exception of the Sertoli elements, within a period of two weeks. The testes became smaller, owing to shrinkage of the tubules, and the interstitial cells apparently were greatly increased in numbers, but actually were only concentrated into smaller areas. Such testicles never again returned to a spermatogenetic function as long as they remained in the abdomen. If they were replaced in the scrotum, while residual spermatogonia yet remained, they would re-establish complete spermatogenetic function. Some important relation existed between the testicle and scrotum. This was further emphasized by the transplantation of testis tissue on the inside of the scrotum and the development of spermatozoa within the graft, the first report of spermatozoon production in a mammalian testis graft.[3]

Our studies on vasoligation also gave unexpected results. With rats, rabbits, guinea pigs and sheep seminiferous tubule degeneration did not follow ligation of the ductus deferens, nor did compensatory hypertrophy of the interstitial cells occur.[7, 8] These results were at variance with essentially all current reports from European laboratories.

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[4] Steinach, E.: Verjungung durch experimentelle Neubelebung der alternden Pubertatsdruse. Arch. f. Entw.-Mech., 46: 557–618, 1920.

[5] Sand, K.: Vasoligature (epididymectomy) employed ad Mod. Steinach with a view to restitution in cases of senium and other states (impotency, depression). Acta Chirurgica Scandinavica, 55: 387–426, 1922.

[6] Moore, C. R.: Testicular reactions in experimental cryptorchidism. Am. J. Anat., 34: 269–316, 1924.

[7] Moore, C. R. and Oslund, R.: Experiments on the sheep testis—cryptorchidism, vasectomy and scrotal insulation. Amer. J. Physiol., 67: 595–607, 1924.

[8] Moore, C. R. and Quick, W. J.: Vasectomy in the rabbit. Am. J. Anat., 34: 317–336, 1924.

Some of the observations forced attention to the question of the influence of the scrotum on spermatogenesis. Why did an adult testis of a guinea pig, that had been removed from the scrotum and confined in the abdomen with all nerves, blood vessels, and ductus deferens intact, begin immediate degeneration and never recover while confined in that locality? Why did testis grafts produce spermatozoa when they were attached to the inside walls of the scrotum, but failed to do so in any other locality? Experiments were carried out that eliminated all suggestions, but one, that appeared to offer a plausible explanation. The final remaining hypothetical cause for the responses could possibly rest on some difference in the temperatures that exist in the abdomen and in the scrotum. This line of thought received some encouragement from a short theoretical paper by Crew[9] who postulated some such possible explanation for the aspermatic testicle located in the abdomen.

An investigation of this possibility involved the use of several procedures. It was learned that a single treatment of a guinea pig by submerging the scrotum in water of a temperature of 6C to 7C above the normal body temperature, for a period of 10 minutes, caused marked degeneration of the spermatogenetic tissue within a period of a few days. Exposures of the scrotum to heat waves from an electric hot plate, light bulb or from diathermy currents applied by electrodes in contact with two sides of the scrotum, or the direct submergence of the testicle through a low abdominal incision in warmed saline solution, all induced extensive degeneration and loss of spermatogenetic tissues. It was evident, therefore, that a slight excess of temperature above that normal for the body was highly injurious to the testicle.[10]

Provided the conception that a difference in temperature between the abdomen and the scrotum was valid, one should be able to demonstrate it. Following considerable delay in obtaining aid in thermocouple determinations, two small local areas on the ventral abdomen were anesthetized and two ordinary 100C laboratory thermometers were inserted, the bulb of one being retained amid the abdominal viscera and the other passed through the inguinal canal into the scrotum alongside the testis. It became evident at once that in unanaesthetized rats, rabbits and guinea pigs observed at room temperatures, the scrotal temperatures were from 2C to 4C lower than those in the abdomen at the same moment; observed at lower than room temperature there was even a greater difference.[11] Thus two points were clearly in favor of a scrotal regulation of temperatures about the testes: a) testes were peculiarly susceptible to temperatures higher than those normal for the body, b) normal scrotal temperatures were actually lower than those in the abdomen at the same moment. The latter finding was very soon confirmed on human patients on the operating table by German observers.[12] One final and presumably conclusive experiment could be arranged to determine the correctness of the implication of a heat regulatory function of the scrotum.

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[9] Crew, F. A. E.: A suggestion as to the cause of the aspermatic condition of the imperfectly descended testis. Jour. Anat. (London), 56: 98–106, 1922.

[10] Moore, C. R.: Heat application and testicular degeneration: The function of the scrotum. Am. J. Anat., 34: 337–358, 1924.

[11] Moore, C. R. and Quick, W. J.: The scrotum as a temperature regulator for the testis. Am. J. Physiol.,68: 70–79, 1924.

[12] Harrenstein, R. J.: Über die funktion des scrotums und die behandling der retentio testis beim Menschen. Zentrlbl. f. Chir., No. 28, 1734–1739, 1928.

The test involved the utilization of large mature rams in which the testicles are permanently confined in the scrotum, and the latter is sufficiently pendent to permit of insulation. The scrotum was loosely encased in a fairly thick layer of woolen batting, carefully, but loosely sewed to fit snugly but without binding. Coverings of waterproofed materials, and a suspensory over the back and hips left the scrotal coverings dry, loosely fitting, and well supported to avoid binding. Histological examination of testicles removed from the scrotum two and one-half months after the application of the insulation revealed that all seminiferous tubules in the organ were in stages of degeneration. The germinal epithelium was in process of disintegration; fragmented and isolated cells were free in the lumen of the tubules, or the tubules were totally empty except for the Sertoli elements. Multinucleate giant cells, that usually characterize involuting or degenerating tubules, were numerous. Such an animal, under these conditions, therefore, had sterilized itself by its own body heat because of the abolishment of the thermo-regulatory function of the scrotum through insulation.[7]

Corrolaries, and proofs of other type, confirm this thermo-regulatory function of the scrotum. Severe febrile states in man are known to be accompanied by azospermia.[13, 14] In Australia it was shown that rams held at sea level during the heat of summer experience loss of spermatogenetic function if running at large in the open, but those confined within a shed, the temperature of which was kept lower than outside temperatures, continued to produce spermatozoa.[15] Phillips and McKenzie[16] applied scrotal insulation to rams trained to mount a dummy and ejaculate. An examination of the seminal discharge each week showed normal spermatozoa prior to application of the scrotal coverings, a loss of sperm from the discharge a few weeks after its application, and a gradual return to a normal seminal discharge a few weeks after removal of the insulation.

The recognition of a thermo-regulatory function of the scrotum, a necessity for the production of mature germ cells, thus explained many of our previous findings. Testis grafts in mammals carry spermatogenesis to the final stage of spermatozoon formation only when located in an environment below that of normal body temperature, such as on the scrotal walls, or in the anterior chamber of the eye.[17] Cryptorchid testes, naturally occurring or artificially produced, lose all spermatogenetic capacity, and vasoligation causes tubular degeneration only when poor surgery, often involving adhesions, leaves the testis exposed to

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[13] Mills, R. G.: The pathological changes in the testes in epidemic pneumonia. J. Exp. Med., 30: 505–529, 1919.

[14] MacLeod, John and Hotchkiss, R. S.: The effect of hyperpyrexia upon spermatozoa counts in man. Endocrinol., 28: 780–784, 1941.

[15] Gunn, R. M. C. and Sanders, R. N.: Seminal changes affecting fertility in sheep. Council for Scientific and Industrial Research, Commonwealth of Australia, Bulletin No. 148, 1942.

[16] Phillips, R. W. and McKenzie, F. F.: The thermo-regulatory function and mechanism of the scrotum. Research Bulletin 217, Missouri Agricultural Experiment Station, 1934.

[17] Turner, C. D.: Intra-ocular homotransplantation of prepuberal testes in the rat. Am. J. Anat., 63: 101–159, 1938.

the higher abdominal temperatures. Application of diathermy to the testis quickly destroys the spermatogenetic tissues. Recovery of spermatogenetic function follows in all such conditions, where corrections are made, provided degeneration has not already removed the residual spermatogonia.

The scrotum is well adapted to serve a thermo-regulatory function because of its special characters. The skin is unusually thin; it is well provided with sudoriporous glands; there is little or no subcutaneous fat or connective tissue; and it is well known that the cremasteric muscle varies in its degree of contraction or relaxation in relation to the temperature.

Thus these collective and varied experiences enabled us for the first time to assign to the scrotum a definite function. The basic information permitted an understanding of many aspects of importance in the normal function of the testis, especially as it related to the production of germ cells.

TESTIS HORMONE INDICATORS: INFLUENCE OF SEX HORMONES

About 1920, a great deal of general interest in the endocrine function of the testis was stimulated by the unsubstantiated claims of Steinach and of Voronoff, but real advances in our knowledge of these problems awaited the successful extraction of the hormone, which in turn required proper methods of detection to follow any activity that might be present in extracts. It had been known since 1849, when Berthold castrated roosters, that the condition of the comb depended upon testis hormone. In mammals, however, no tests for the detection of hormones from the testis within reasonably short working periods had been developed. Our further pursuit of the problem of the effect of temperature on germ cells (spermatozoan) after their formation, unexpectedly introduced one workable procedure, applicable to the guinea pig, that was called the spermatozoon motility test; it was the first hormone indicator method applied to the mammal for testing extracts for the presence of hormone.

It was found that spermatozoa in the cauda epididymis, so isolated that additional sperm could not enter, would remain alive and retain their capacity for motility for periods up to more than 60 days, provided hormone was being secreted into the animal body by at least one testis. Without testis hormone secretion this capacity for motility was retained for less than 30 days.[18]

The discovery of this hormone detection method occurred just at the time when McGee[19] had been able to prepare extracts from bull testes that exerted a comb-growth stimulation when injected into capons. We were able to show that the same impure extracts of bull testes that stimulated comb-growth, increased the length of time that spermatozoa in an isolated epididymis of the guinea pig retained their capacity for motility.[20] This finding gave increased assurance that the impure extracts of bull testes actually contained the active male hormone. This encouragement led, through a combined and joint study could be arranged to determine the correctness of the implication of a heat regulatory function of the scrotum.

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[18] Moore, C. R.: Spermatozoon activity and the testis hormone. J. Exp. Zool., 50: 455–494, 1928.

[19] McGee, L. C.: The effect of the injection of a lipoid fraction of bull testicle in capons. Proc. Inst. Med. (Chicago), 1927.

[20] Moore, C. R. and McGee, L. C.: On the effects of injecting lipoid extracts of bull testes into castrated guinea pigs. Am. J. Physiol., 87: 436–446, 1928.

The test involved the utilization of large mature rams in which the testicles are permanently confined in the scrotum, and the latter is sufficiently pendent to permit of insulation. The scrotum was loosely encased in a fairly thick layer of woolen batting, carefully, but loosely sewed to fit snugly but without binding. Coverings of waterproofed materials, and a suspensory over the back and hips left the scrotal coverings dry, loosely fitting, and well supported to avoid binding. Histological examination of testicles removed from the scrotum two and one-half months after the application of the insulation revealed that all seminiferous tubules in the organ were in stages of degeneration. The germinal epithelium was in process of disintegration; fragmented and isolated cells were free in the lumen of the tubules, or the tubules were totally empty except for the Sertoli elements. Multinucleate giant cells, that usually characterize involuting or degenerating tubules, were numerous. Such an animal, under these conditions, therefore, had sterilized itself by its own body heat because of the abolishment of the thermo-regulatory function of the scrotum through insulation.[7]

Corrolaries, and proofs of other type, confirm this thermo-regulatory function of the scrotum. Severe febrile states in man are known to be accompanied by azospermia.[13, 14] In Australia it was shown that rams held at sea level during the heat of summer experience loss of spermatogenetic function if running at large in the open, but those confined within a shed, the temperature of which was kept lower than outside temperatures, continued to produce spermatozoa.[15] Phillips and McKenzie[16] applied scrotal insulation to rams trained to mount a dummy and ejaculate. An examination of the seminal discharge each week showed normal spermatozoa prior to application of the scrotal coverings, a loss of sperm from the discharge a few weeks after its application, and a gradual return to a normal seminal discharge a few weeks after removal of the insulation.

The recognition of a thermo-regulatory function of the scrotum, a necessity for the production of mature germ cells, thus explained many of our previous findings. Testis grafts in mammals carry spermatogenesis to the final stage of spermatozoon formation only when located in an environment below that of normal body temperature, such as on the scrotal walls, or in the anterior chamber of the eye.[17] Cryptorchid testes, naturally occurring or artificially produced, lose all spermatogenetic capacity, and vasoligation causes tubular degeneration only when poor surgery, often involving adhesions, leaves the testis exposed to

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[13] Mills, R. G.: The pathological changes in the testes in epidemic pneumonia. J. Exp. Med., 30: 505–529, 1919.

[14] MacLeod, John and Hotchkiss, R. S.: The effect of hyperpyrexia upon spermatozoa counts in man. Endocrinol., 28: 780–784, 1941.

[15] Gunn, R. M. C. and Sanders, R. N.: Seminal changes affecting fertility in sheep. Council for Scientific and Industrial Research, Commonwealth of Australia, Bulletin No. 148, 1942.

[16] Phillips, R. W. and McKenzie, F. F.: The thermo-regulatory function and mechanism of the scrotum. Research Bulletin 217, Missouri Agricultural Experiment Station, 1934.

[17] Turner, C. D.: Intra-ocular homotransplantation of prepuberal testes in the rat. Am. J. Anat., 63: 101–159, 1938.

the higher abdominal temperatures. Application of diathermy to the testis quickly destroys the spermatogenetic tissues. Recovery of spermatogenetic function follows in all such conditions, where corrections are made, provided degeneration has not already removed the residual spermatogonia.

The scrotum is well adapted to serve a thermo-regulatory function because of its special characters. The skin is unusually thin; it is well provided with sudoriporous glands; there is little or no subcutaneous fat or connective tissue; and it is well known that the cremasteric muscle varies in its degree of contraction or relaxation in relation to the temperature.

Thus these collective and varied experiences enabled us for the first time to assign to the scrotum a definite function. The basic information permitted an understanding of many aspects of importance in the normal function of the testis, especially as it related to the production of germ cells.

TESTIS HORMONE INDICATORS: INFLUENCE OF SEX HORMONES

About 1920, a great deal of general interest in the endocrine function of the testis was stimulated by the unsubstantiated claims of Steinach and of Voronoff, but real advances in our knowledge of these problems awaited the successful extraction of the hormone, which in turn required proper methods of detection to follow any activity that might be present in extracts. It had been known since 1849, when Berthold castrated roosters, that the condition of the comb depended upon testis hormone. In mammals, however, no tests for the detection of hormones from the testis within reasonably short working periods had been developed. Our further pursuit of the problem of the effect of temperature on germ cells (spermatozoan) after their formation, unexpectedly introduced one workable procedure, applicable to the guinea pig, that was called the spermatozoon motility test; it was the first hormone indicator method applied to the mammal for testing extracts for the presence of hormone.

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[18] Moore, C. R.: Spermatozoon activity and the testis hormone. J. Exp. Zool., 50: 455-494, 1928.

[19] McGee, L C.: The effect of the injection of a lipoid fraction of bull testicle in capons. Proc. Inst. Med. (Chicago), 1927.

[20] Moore, C. R. and McGee, L. C.: On the effects of injecting lipoid extracts of bull testes into castrated guinea pigs. Am. J. Physiol., 87: 436-446, 1928.

The perfection of extraction methods by the biochemists for male hormone, from both fresh testis tissue and from male urine,[26] its chemical analysis[27] and ultimate synthesis,[28, 29] coupled with dependable test methods, permitted the study of conditions under which the testis secreted its hormone and some of the effects the hormone exerted in the reproductive life of mammals in general and man in particular.

It is a truism that all advances in our knowledge of the organism depend to a large extent upon the utilization of stepping stones contributed by earlier investigations. In this respect advances in our knowledge of the male hormone were aided tremendously by information gained through studies on the female hormone, and especially from studies on the gonadotrophic activity of the pituitary gland. The work of Smith[30, 31, 32] and Smith and Engle[33] clearly demonstrated the absolute dependence of the gonads upon pituitary secretions for their structural and functional welfare. These advances, made by others, were utilized in many ways in connection with our studies on the effects of male hormone preparations in the animal body.

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[21] Moore, C. R. and Gallagher, T. F.: Seminal-vesicle and prostate function as a testis-hormone indicator; the electric ejaculation test. Am. J. Anat., 45: 39–69, 1930.

[22] Moore, C. R., Price, D. and Gallagher, T. F.: Rat-prostate cytology as a testis-hormone indicator and the prevention of castration changes by testis-extract injections. Am. J. Anat., 45: 71–107, 1930.

[23] Moore, C. R., Hughes, W. and Gallagher, T. F.: Rat seminal-vesicle cytology as a testis-hormone indicator and the prevention of castration changes by testis-extract injection. Am. J. Anat., 45: 109–135, 1930.

[24] Vatna, S.: Rat vas deferens cytology as a testis hormone indicator and the prevention of castration changes by testis extract injections. Biol. Bull., 58: 322–335, 1930.

[25] Heller, R. E.: Cowper's gland as a testis hormone indicator. Proc. Soc. Exp. Biol. & Med., 27: 751–752, 1930.

[26] Koch, F. C.: The biochemistry of androgens. In Sex and Internal Secretions, Williams and Wilkins Co., 1939, 2nd ed., chapt. 12.

[27] Butenandt, A. and Tscherning, K.: Über Androsterone II. Seine chemische Charakterisierung. Ztschr. f. physiol. Chem., 229: 185, 1934.

[28] Butenandt, A. and Hanisch, G.: Uber Testosteron. Ztschr. f. physiol. Chem., 237: 89, 1935.

[29] Ruzicka, L., Wettstein, A. and Kagi, H.: Darstellung von Testosteron unter Adwendung gemischter Ester. Helv. chim. Acta, 18: 1478, 1935.

[30] Smith, P. E.: The disabilities caused by hypophysectomy and their repair. J. Am. Med. A., 88: 158–161, 1927.

[31] Smith, P. E.: The induction of precocious sexual maturity by pituitary homeotransplants. Am. J. Physiol., 80: 114–125, 1927.

[32] Smith, P. E.: Hypophysectomy and a replacement therapy in the rat. Am. J. Anat., 45: 205–274, 1930.

[33] Smith, P. E. and Engle, E. T.: Experimental evidences regarding the role of the anterior pituitary in the development and regulation of the genital system. Am. J. Anat., 40: 159–217, 1927.

Our utilization of the potent, but impure, extracts of bull testes, prepared by the biochemists, revealed some of the effects of male hormone injections into both normal and castrate laboratory animals; these effects were later substantiated when the pure chemical hormones were available for use. The accessory reproductive organs (prostate gland, Cowper's gland, seminal vesicles, ductus deferens, etc.) which exhibited rapid involution, and loss of secretory capacity following castration, were completely repaired by testis extracts and returned to the normal secretory condition whether castration had been carried out in prepuberal ages or in adult life. Treatment of normal males of prepuberal, or postpuberal, ages either hastened the secretory development of the accessory, or target organs, or stimulated markedly the increase in organ size, and intensity of secretion. That male hormones could not be regarded as stimulating to the entire reproductive system was quickly shown by the injurious effects upon the testicle. The effects, particularly conspicuous during the phase of rapid growth and attainment of spermatogenesis, included the disruption of tubules and the sloughing of the cells of the spermatogenetic tissues, and a reduction in size of the testicle from one-third to one-half the fresh weight of the testicle of untreated controls.

Female hormones when injected into normal males likewise caused marked degeneration and reduction in size of the testicles, but unlike the stimulating effects of male hormone on accessory organs, female hormones caused the rapid loss of secretory functions in these structures; the prostate and Cowper's glands, and seminal vesicles were converted into a castrate condition as readily and effectively as by removal of testes. It may be recalled that Steinach and Lipschutz had long contended for an antagonistic action between hormones from the two sexes. The demonstration, however, that female hormones were injurious to the ovary as well as to the testis, and that male hormone induced testicular injury of a similar character to that induced by female sex hormones, required a modification in the interpretation of hormone effects within the organism. Male and female hormones could be mixed in the same solution in physiological dosages without the nullification of the effects of either. Our experiments showed further than injurious effects of daily estrogen dosages in guinea pigs were avoided by the occasional implantation of fresh pituitary tissue along with the estrogen treatment.[34, 35]

Thus it gradually became apparent that the injurious effects of hormones on the gonads was an indirect effect that involved the activity of the pituitary gland. Secretions from the pituitary are required for both the gametogenetic and endocrine function of the gonads, and at the same time the production and release of these pituitary secretions are held in check as the titre of gonadal secretions in the blood stream is increased; neither gonads nor pituitary carry on a maximum function under normal conditions and the reciprocal influences

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[34] Moore, C. R.: A critique of sex hormone antagonism. Proc. 2nd Internat. Congress for Sex Research, London, pp. 293–303, 1930.

[35] Moore, C. R. and Price, D.: Gonad hormone functions, and the reciprocal influence between gonads and hypophysis with its bearing on the problem of sex hormone antagonism. Am. J. Anat., 50: 13–71, 1932.

involved constitute one of the controlling mechanisms of the living organism (see Moore and Price[35]). These functional interactions involving gonadal activity, target organ response, and pituitary function constitute the basic premises of the Huggins' treatment for prostatic carcinoma. Special conditions are likewise involved in the regulation of the cyclic nature of reproduction whether on an annual or shorter term intermittent cycle basis. It may be mentioned in passing that the reciprocal action phenomena exhibited by the gonads and pituitary as a regulating mechanism likewise apply to other endocrine regulations. This follows for regulation of thyroid secretions, adrenal activities, and to some extent at least for parathyroid function. In general it will be found that the introduction of an endocrine secretion into the body will result in an injury and involution of the organ which produces the product.

THE PROBLEM OF EMBRYONIC SEX HORMONES

The original direction of our interests to the freemartin problem was left dangling farther back in this discourse but during the progress of these side investigations additional attention was given to that study. Attempts to produce a freemartin included, among others, the injection of impure male hormone extracts into embryos, or into pregnant mothers, and later the use of pure chemical hormones when these became available. Up to the present time, however, no one of the many investigators in this field has succeeded in duplicating the freemartin condition that was produced for us originally in one of nature's own experiments. A more detailed account of the various approaches employed in attempts to produce freemartin conditions in all the different classes of vertebrates has been presented elsewhere.[36]

It is sufficient to state for this occasion that the utilization of the sexually undifferentiated pouch young of the American opossum for treatments with sex hormones during their sexual differentiation in the marsupial pouch have led me to question the correctness of the freemartin hypothesis. Direct treatment of the developing young during sexual differentiation, rather than the indirect treatment by way of the pregnant mother, has produced modifications in its sexual differentiation, but on the whole these have not been of the character expected from the hypothesis. The results suggest that we may be forced to seek other explanations for the freemartin, and for normal sexual differentiation, different from those that prevailed 34 years ago. The freemartin condition is still an unsettled problem but in the pursuit of attempts to understand it, our attention, as I have suggested, has been diverted from time to time to problems that arose secondarily. The original problem of the basic controls of sexual differentiation is still much in the forefront and, indeed, is a subject that within a week will have the attention of an international group in Paris. It is hoped that these previous failures to accomplish the original intent to produce freemartin conditions by experiment, and to gain an understanding of the forces involved in sexual differentiation, may have at least yielded a few worthwhile by-products.

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[36] Moore, C. R.: Embryonic sex hormones and sexual differentiation. Springfield: Charles C. Thomas, 1947.

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WRITING A MEDICAL PAPER: WHY AND HOW

MILEY B. WESSON

The purpose of this article is to encourage young physicians to write medical papers and to write them well. It is directed primarily to the man who writes his own papers. Many English physicians, when they begin to study medicine, have had the advantage of a sound literary background, while many less-blest American physicians find difficulty in organizing their ideas and presenting them in intelligible form. A large lucrative practice does not mean that one can write a good paper; and neither do knowledge and intelligence suffice to make a good writer. Three pertinent questions arise: Why write a paper? What about? and How?

When a man starts to practice he is likely to have free time. Hugh H. Young taught that the only way a neophyte can force himself to study is to prepare a paper. This is one good motive for writing a medical paper: it provides a stimulus to study.

The highest purpose in publishing a scientific article is, of course, the sharing of worthwhile information. Incumbent on every physician who discovers scientific facts, who sees new relationships of old ideas or data, who has carefully studied a given subject, given it thought, who has the broad point of view and wide experience in his field, who has completed a productive research project, is the responsibility of passing on his knowledge to others who may find use for it. This dissemination of knowledge is essential to medical progress.

Also, the only way a doctor can ethically advertise, aside from appearing on medical programs, is by publishing good medical papers, or papers of popular interest. If you do not agree, look in a California newspaper that is on a medical school "clip sheet" list, or the current issues of *Time* and *Newsweek*.

What are you going to write about? Original observations should be published. An unusual case report is a sufficient nucleus for a paper. When a careful analysis of pertinent data in the literature is added, a worthwhile offering develops. A good paper based on a single case report will attract attention, whereas a "big" paper, even though it has hidden away in it an original procedure, will be passed over by the reviewer; anything published without a title which will be listed in the *Quarterly Cumulative Index Medicus* is buried and lost. In general, your clinical experience and interests will offer you adequate material. You may have found practical time-saving shortcuts worth recording. Take the time to investigate and develop the ideas that occur to you as you are seeing patients.

The methods of writing a paper are, to a degree, individual. Some general suggestions, however, may help in organizing the material and in making it suitable for publication. First, study the material you have and on this basis formulate an orderly outline. The preliminary organization and recording are elementary and essential; the outline used in Osler's *Practice of Medicine* is a good one.

You will want to read as extensively as possible. The simplest procedure is to

Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 9, 1950.

start with the *Quarterly Cumulative Index Medicus*, the Surgeon General's Index Catalog, and the subject index of the *Journal of Urology*. These will give you a start, and the reference lists of the articles indexed there will carry you on. These lists should not be considered to be all-inclusive. For recent articles not covered therein, the tables of contents of the current journals offer the only solution. If you claim a review of the literature, it will probably be necessary to read or scan hundreds of articles. In most instances it is necessary to use only those articles with relevant information. An iconoclastic attitude in reviewing the literature is important.

While you have the journals at hand, list the complete information to be used as a reference. A card system is probably the most practical. This may save you hours in the library running down the same article a second time. Record the author's name, the complete title, the journal, the volume, inclusive pages, month and year. It is neither wise nor honest to refer to the original article if you have used an abstract, indirect quotation or translation. As you make notes from these articles clearly indicate the source.

With this material—the information you wish to present and the outline—begin the first draft. The mark of a great writer is to say uncommon things in common ways. Sir William Osler, although his short intelligible papers in simple English do not show the signs of effort, often rewrote his papers six or eight times in longhand before they were typed for the first time. Sir Clifford Allbutt thought it reasonable to go over a paper about nine times. Tolstoy said, "I cannot understand how anyone can write without rewriting everything over and over again," and Mark Twain added, "The difference between the right word and the almost right word is the difference between lightning and the lightning bug." Eliminate ruthlessly all irrelevancies, no matter how interesting. Save them for another time. Emulate Flaubert, who said, "I have just suppressed phrases which cost me the entire work of many days."

A simple clear presentation is a worthwhile accomplishment. Dr. William H. Welch told his classes that almost all of the great discoveries in medicine were reported in articles of less than 3,000 words, ten or twelve typewritten pages, double-spaced. (There is a growing tendency to prepare two papers, one to publish and the other, a 10 minute paper, to read. In the latter, dry facts are eliminated and statements that will hold the auditors' attention substituted.)

However, accuracy and clarity should not be sacrificed in an attempt to achieve brevity. You owe your reader a complete explanation. Short sentences are easier to understand than long ones.

The title is important. It must be descriptive and as brief as possible. Bear in mind that the words you choose will be used by indexers. If the nouns are well chosen the paper will be listed in the *Quarterly Cumulative Index Medicus* under three or four headings.

The introduction should state clearly the nature, content and scope of the material which follows. Touch the keynote, indicate what may be expected.

The summary should give the salient features as concisely as possible. These are frequently used verbatim by abstracters. Because of the large volume of medical literature, most readers, after a glance at the title and author's name, turn to the summary. If it gives promise of something interesting they will read the article.

Conclusions are general statements of truths established in the paper, and are not warranted unless the paper is conclusive. Conclusion in this sense does not refer simply to the end of the paper.

The exact title, the introduction and summary are often written after the paper is otherwise finished.

The great faults of medical writing are verbosity, lack of clarity and paucity of worthwhile information. Limit the historical discussion to not more than half a page when possible. In case reports (identified by the hospital or office file numbers) use only pertinent facts. If a report is interesting and correspondingly long, give an epitome in the first line and at the end add a short paragraph as a summary, so that the reader will not skip the report in its entirety. If there are a number of similar case reports, group the extra ones in a single paragraph.

To urge medical school graduates to review the simple rules of grammar may seem absurd, but reading "finished" manuscripts for 38 years leaves no alternative. The minimum reference books as to style are *Webster's New International Dictionary*, *The American Illustrated Medical Dictionary*, the *Secretary's Handbook*, and *Words into Type*.

Do not repeat the same sentence structure nor begin every sentence with *there are*. Rather use repetition as an aid to emphasize. Since few exact synonyms exist it is well to be aware of the subtle shades of meaning before using words interchangeably.

Every sentence should have a subject and a predicate, and the use of nouns and adjectives as verbs is merely medical jargon. Cases do not *hemorrhage*, nor are they *x-rayed*, *cystoscoped*, or *operated*. As deplorably as the word *case* is misused for *patient*, is *theory* for *guess, surmise, impression, opinion* or *idea*, and *speculation* for *notion* or *view*.

The needless repetition of *I* should be avoided, but the use of the naked *I* is no longer considered immodest. It is sometimes less awkward and more honest to use it than to refer to oneself as the *author*. If the antecedent of *we* is clearly indicated and maintained throughout the paper, it is a useful pronoun, but if the antecedents include mankind in general, the people of the United States, all physicians, the members of this specialty, and I, the author, the reader has a right to be confused and annoyed.

The purpose of the tense of verbs is to express time relationships. Change tense in the course of a sentence or a paragraph only when necessary. Experimental facts and case reports should be given in the past tense. Discussion of results may be in both past and present tense, and accepted truths should be stated in present tense.

It is permissible to occasionally split an infinitive if clearness, smoothness or force would otherwise be lost. To forbid the ending of a sentence with a preposition is pedantic. Better a smooth clear forceful sentence than an awkward one.

The relative pronouns *who, which* and *that* are frequently misused. *Who* refers to persons, *which* to animals or inanimate articles, and *that* to persons, animals or things.

Whom is often misused for *who* because the writer fails to realize that the relative pronoun is the subject of the following verb, not the object of the preceding preposition or verb; the whole relative clause may be the subject.

Remember Professor Nuttall's warning to watch your *thats, ands, buts, whiles,* and *sinces;* they multiply like bacteria.

Abbreviations and contractions are merely forms of shorthand and most of them are undesirable in published longhand; *e.g., i.e.,* and *viz.,* for instance, should be written out. Contractions for names of diseases and methods should not be used.

A sentence should never begin with a figure. Otherwise the tendency is toward using figures rather than spelling out numbers. Some publishers prefer to spell out those that can be expressed in one or two words.

Spell out the name of the month in full, and use figures for the days, omitting d, th, st; for example, October 12, 1950. The number of the year should be written in full: 1897, not '97; 1897–8 is preferable to either 1897–1898 or 1897–98.

Never capitalize chemicals, drugs and anatomical parts, except of course, at the beginning of sentences, irrespective of whether they are brand names or derived from proper nouns; with few exceptions this holds for diseases. Follow Bergey's *Manual of Determinative Bacteriology* for the names of micro-organisms.

Punctuate to clarify sentence structure, and to avoid ambiguity. Commas are used to prevent misreading. Use a comma before *and,* or *or* in a series as "biology, chemistry, or physics." Put a comma before a complete statement introduced by *and, but, for, or, nor* or *neither.* Commas may supplant *and, but,* or *as,* while a semicolon may take the place of *therefore.* However, a semicolon or a period should be used if the statements are long or complicated.

Place a period or semicolon, never a comma, before a complete statement introduced by *however, yet, still, nevertheless, therefore, so hence, moreover, further, accordingly, besides, also, thus, then, indeed,* and *otherwise.*

The colon may be said to replace *that is,* or *for example.* The first word after a colon is often capitalized when it begins a complete passage or a sentence. The combination of a semicolon or colon and a dash is obsolete.

When closing quotation marks fall alongside a comma or a period, set the comma or period inside the quotation. But if the comma or period is not part of the quotation, place it outside the quotation marks.

Denote excerpts by enclosing them in quotation marks. An excerpt of more than one paragraph should have open quotation marks before each paragraph and closing quotation marks at the end of the last paragraph. A quotation within a quotation should be enclosed in single quotation marks. If the quotation begins in the middle of a sentence, the fact is sufficiently indicated by writing the first word with a small letter. Omissions from a quotation must be indicated by three full stops or periods separated by spaces (. . .).

Illustrations, tables and charts should save, not repeat, a thousand words of text. Every illustration should have a purpose; it is not inserted for its beauty; it must earn its place. Simple appropriate legends should accompany illustrations. These should be typed together on a separate sheet of paper, because the photograph goes to the photo-engraver and the legend to the printer. Tables and charts should also be submitted on separate sheets, not in the text. On the back of each print should be marked with light pencil—the figure number, "top," and the name of the author. Arrows should be small. Use only India ink for pen sketches.

Color reproductions are expensive. Kodachrome or other transparency costs are about 50 per cent higher than an original drawing. If the colors on the transparency are thin, the price is even higher. The cost of an average color plate may easily equal the cost of a good second-hand automobile.

X-ray film copies should be shiny prints, 5 by 7 inch negatives. Indicate where film may be cropped, but leave the localizing landmarks. For instance, a kidney picture should show the pelvic brim, twelfth rib and part of the vertebral column. To emphasize the pyelogram and avoid retouching, make a rough diagram on tissue paper of the proposed print, and with a wax or skin pencil, blot out all of the areas not needing emphasis; superimpose and photograph through this. If the film is thin use a red skin (wax) pencil; if it is medium thick, use black. Red holds back more light than black. Then, overexpose and underdevelop to make less contrast. Pathological specimens should be photographed with a ruler to show size. Be sure that the ruler carries no advertising.

If, during the preparatory note-taking, references are properly recorded, compiling the bibliography will be simple. The name of the journal must be abbreviated according to the style of the *Quarterly Cumulative Index Medicus* (a booklet listing these has been prepared for the *Journal of Urology*). There are different correct methods of preparing bibliographies. The Waverly Press, which prints over 100 journals, recommends the following style:

"Jones, J. R. and Smith, P. T.: Q Fever in the Arctic Areas. Am. J. Hyg., 44: 6–22, 1946."

When the author's name is given in the text, some prefer footnote references, but if the reference list is arranged in alphabetical order the information wanted can be easily found. A bibliography should rarely exceed one page; hence, if a complete survey of the literature is made, key articles should be used that list many articles. However, if a quotation is used, the article must be listed in the bibliography. Text books rarely belong in a bibliography. Although many titles indicate little, the title is of value because it reflects the nature and scope of the article. To one who has encountered inaccurate references and spent hours trying to find nonexistent articles in nonexistent journals, there is little need to re-emphasize that accuracy is important.

When you have completed what you consider a satisfactory draft of your masterpiece, lay it aside for at least two weeks. During the interim, think about what you have written. It may be worthwhile to ask one of your associates to check through it quickly to see that your meaning is clear. Then, read the paper again and you may be surprised to find what a miserable, verbose article it is. Begin again. Transfer the sentences that are out of place and that you want to keep, and place them where they belong (a pair of shears and paper of pins are invaluable). Smooth out the rough spots and rewrite the paper around them, and then again lay it aside.

Do not wait to make revisions on the galley proof. To delete a ten-letter word from the first line of a fifteen-line paragraph costs the *Journal of Urology* more than the price of a carton of cigarettes.

SUMMARY

This paper is a brief exposition of the reasons for writing a medical paper, of selection of suitable subjects and some suggestions for the preparation of manuscript for publication. The technique of assembling the material, preparing the copy, and prints of pyelograms are described, and the desirability of rewriting is emphasized.

490 Post St., San Francisco 2, Calif.

REFERENCES

Allbutt, T. Clifford: Notes on the Composition of Scientific Papers. London: Macmillan & Co., 1923.
Allen, Jr., William E.: Medical Writing: Information for Authors. J. Nat. M. A., 40: 18–23, 1948.
Alvarez, Walter C.: Proc. Staff Meet. Mayo Clinic, 24: 442–444, 1949.
Bergey's Manual of Determinative Bacteriology. Baltimore: Williams & Wilkins Co., 1948.
Bodmer, Fred.: The Loom of Language. New York: W. W. Norton & Co., 1944.
Bowers, Warner F.: Medical Public Speaking. Bull. U. S. Army, M. Dept., 9: 467–476, 1949.
Brittain, Robert: Punctuation. A Practical Method Based on Meaning. New York: Barnes & Noble, Inc. 1950.
Ellis, Albert: The application of scientific principles to scientific publications. Scient. Monthly, 66: 427–430, 1948.
Fishbein, Morris: Medical Writing; the Technic and the Art. Philadelphia: Blakiston Co. 1948.
Flesch, Rudolph: The Art of Plain Talk. New York: Harper & Bros., 1946.
Golden, Ross: Comments on the preparation and presentation of medical papers. Am. J. Roentgenol., 55: 495–502, 1946.
Hewitt, Richard M.: Better medical writing: Some typical errors and how to avoid them. J. Urol., 40: 454–463, 1938.
——: Writing and presentation of medical papers: Some suggestions. Mississippi Valley M. J., 71: 22–25, 1949.
Kapp, Reginald O.: The Presentation of Technical Information. London: Constable & Co., 1948.
Kies, Paul A.: A Writer's Manual and Work Book. New York: F. S. Crofts & Co., 1936.
List of Abbreviations, Index-Catalogue, Fourth Series, Army Medical Library, 1948.
A Manual of Style. Chicago: The University of Chicago Press, 1949.
Merrill, Paul W.: The principles of poor writing. Scient. Monthly, 64: 72–74, 1947.
Nuttall, G. H. F.: Notes on the preparation of papers for publication in the Journal of Hygiene and in Parasitology. J. Hyg., 40: 1–62, 1940.
Preparation of Manuscripts. The Editors of The Journal of Urology (Hugh H. Young), Baltimore, Waverly Press.
Review of John B. Murphy Surgical Clinics, vol. 2. Am. J. Med. Sc., 147: 442–443, 1914.
Rupel, Ernest: Medical English. J. Urol., 45: 664–668, 1941.
Stillman, J. D. B.: Medical literature in California. Pac. Med. & Surg. J., 3: 97–102, 1860.
Skillin, Marjorie E., Gay, Robert M., et al.: Words into Type. New York: Appleton-Century-Crofts, Inc., 1948.
Stevens, Neil E.: The moral obligation to be intelligible. Scient. Monthly, 70: 111–115, 1950.
Taintor, Sarah Augusta and Monroe, Kate M.: The Secretary's Handbook. New York: The Macmillan Co., 1942.
Trelease, Sam F.: The Scientific Paper: How To Prepare It, How To Write It. Baltimore: Williams & Wilkins Co., 1947.
Walters, Waltman: Writing papers on surgical subjects. Mississippi Valley M. J., 71: 26–30, 1949.
Weseen, Maurice H.: Crowell's Dictionary of English Grammar. New York: Thomas Y. Crowell, 1928.
Wilbrecht, Esther I.: Why write a scientific paper. Am. J. M. Technol., 15: 215–221, 1949.
Woolleys, Edwin C.: Handbook of Composition. Boston: D. C. Heath & Co., 1920.

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THE LOWER NEPHRON SYNDROME IN CHILDREN

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Acute renal insufficiency due to lower nephron nephrosis is a clinical syndrome which may be the result of numerous etiologic agents. Although the condition was known several years before, interest was not revived until Bywaters[1] and other British workers reported large numbers of cases resulting from crush injury during the recent war. The term "lower nephron nephrosis" was proposed only recently by Lucké.[2] In children, the syndrome may be seen following transfusion reactions,[3,4] severe burns,[5,6] crushing injuries,[1,7,8,9,10] poisons,[2] and sulfonamide reactions.[11,12,13]

CLINICAL PICTURE

Irrespective of the causative condition, the clinical features are similar. There is usually an initial period of some degree of shock. Nausea, vomiting, weakness, malaise and pain in the abdomen or costovertebral angles may be noted. This may be followed by a slowly developing oliguria and anuria, or sudden anuria. Because of the severity of the manifestations of the causative condition, the anuria may be overlooked in the early stages. In oliguria, the urine may be grossly bloody or smoky in color, with marked acidity, and a fixed specific gravity of about 1.010. There is usually proteinuria, and the urine contains pigmented and cellular casts. After there is complete renal shutdown, there may be a moderate degree of hypertension; nonprotein nitrogen levels rise; edema may become apparent; acidosis develops; and terminally there may be pulmonary edema. In some cases, particularly those of crush injuries and burns, a high serum potas-

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[1] Bywaters, E. G. L.: Ischemic muscle necrosis. J. A. M. A., 124: 1103–1109, 1944.

[2] Lucké, B.: Lower nephron nephrosis. Military Surg., 99: 371–395, 1946.

[3] Burwell, E. L., Kinney, T. D. and Finch, C. A.: Renal damage following intravascular hemolysis. New Eng. J. Med., 237: 657–664, 1947.

[4] DeNavasquez, S. J.: The excretion of hemoglobin, with special reference to "transfusion" kidney. J. Path. & Bact., 51: 413–425, 1940.

[5] Goodpasture, W. E., Levenson, S. M., et al.: Clinical and pathologic study of kidney in patients with thermal burns. Surg., Gynec. & Obst., 82: 652–670, 1946.

[6] Martineau, P. C. and Hartman, F. W.: The renal lesions in extensive cutaneous burns. J. A. M. A., 134: 429–436, 1947.

[7] Corcoran, A. C. and Page, I. H.: Crush syndrome: Post-traumatic anuria. J. A. M. A., 134: 436–441, 1947.

[8] Davidson, C. S. et al.: Medical shock. New Eng. J. Med., 234: 279–288, 1946.

[9] Mallory, T. B.: Hemoglobinuric nephrosis in traumatic shock. Am. J. Clin. Path., 17: 427–443, 1947.

[10] Moloney, W. C., Stovall, S. L. and Sprong, D. H., Jr.: Renal damage due to ischemic necrosis. J. A. M. A., 131: 1419–1421, 1946.

[11] Foy, H., Gluckman, J. and Kondi, A.: Pigment metabolism and renal failure in acute sulfonamide hemolysis resembling black water fever. Trans. Roy. Soc. Trop. Med. & Hyg., 36: 197–238, 1943.

[12] Kleiman, A. H.: Sulfathiazole anuria with recovery following renal decapsulation. J. Urol., 55: 598–601, 1946.

[13] Murphy, F. D., Kuzma, J. F., Polley, T. Z. and Grill, J.: Clinoco-pathologic studies of renal damage due to sulfonamide compounds. Arch. Int. Med., 78: 433–443, 1944.

sium level may be found.[1,14] The critical period is from the seventh to the fourteenth day. When diuresis occurs, it may result in depletion of body water, sodium, and chlorides. The mortality rate is high; the survival rate varies between 10 and 30 per cent. As far as is known, those who survive do not experience residual disturbances in renal function.[3]

Lucké,[2] Mallory[9] and others[6,15,16] have described the pathological picture. Grossly, the kidney is large and swollen, and the cortex is pale; the medulla is dark colored. Essentially, the histologic picture is that of selective destruction and necrosis of the epithelial lining of the distal convoluted tubules and the ascending limb of the loop of Henle. Little or no change is noted in the glomeruli. Some of the distal convoluted tubules may show deposits of heme pigments. Interstitial edema, and perivascular and interstitial lymphocytic infiltration are prominent. Re-epithelialization occurs within two weeks of onset.

PATHOGENESIS

Most writers agree that the pathogenesis of the renal lesion is due to ischemia, resulting from renal vasoconstriction occurring in early shock.[1,9,17,18] It is known that renal vasoconstriction is one of the body's most important mechanisms for maintaining circulating blood volume to combat shock. The Trueta "shunt" may explain this.[19,20] The kidney is capable of withstanding complete ischemia for 30 minutes without damage, but if prolonged to two or three hours, the tubular epithelium suffers severe damage.[21,22] Renal failure persisting after recovery from shock, is due to renal damage.

There is disagreement as to the mechanism for development of the anuria. Some writers believe that heme compounds precipitated in the distal tubules mechanically block urine excretion. It is thought that as the pH of the glomerular filtrate falls and the tubules concentrate the filtrate, hematin is precipitated.[23] The deposited pigments may increase tubular damage.[16] Lucké[2] and Phillips[22] are of the opinion that the lower tubular portions of the nephron, as a result of ischemia, become essentially parchment-like insofar as selectivity of reabsorption is concerned. As a result, the glomerular filtrate passes down the tubules and

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[14] Martin, H. E., Wertman, L. W., Simonson, D. G. and Mehl, J. W.: Clinical potassium problems. Calif. Med., 72: 133–141, 1950.

[15] Marshall, D. and Hoffman, W. S.: The nature of the altered renal function in lower nephron nephrosis. J. Lab. & Clin. Med., 34: 31–39, 1949.

[16] Shen, S. C. and Ham, T. H.: Studies on destruction of red blood cells: Mechanisms and complications of hemoglobinuria, etc. New Eng. J. Med., 229: 701–713, 1943.

[17] Moon, V. H.: Renal deficiency associated with shock. J. A. M. A., 134: 425–429, 1947.

[18] Van Slyke, D. D.: The effects of shock on the kidney. Ann. Int. Med., 28: 701–722, 1948.

[19] Trueta, J., Barklay, A. E., et al.: Studies of the Renal Circulation. Oxford: Blackwell Scientific Pub., 1947.

[20] Goodwin, W. E., Sloan, R. D. and Scott, W. W.: "Trueta" renal vascular shunt. J. Urol., 61: 1010–1027, 1949.

[21] Hamilton, P., Phillips, R. A. and Hiller, A.: Duration of renal ischemia required to produce anuria. Am. J. Physiol., 152: 517–522, 1948.

[22] Phillips, R. A. and Hamilton, P. B.: Effect of 20, 60 and 120 minutes of renal ischemia on glomerular and tubular function. Am. J. Physiol., 152: 523–530, 1948.

[23] Gilligan, D. R., Altschule, M. D. and Katersky, E. M.: Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions. J. Clin. Investigation, 20: 177–187, 1941.

diffuses unaltered back into the circulation, so that there is almost complete reabsorption of glomerular filtrate. That which is not reabsorbed is passed as minute amounts of urine with approximately the same specific gravity as glomerular filtrate or 1.010. Azotemia occurs gradually, as a result of tubular reabsorption of glomerular filtrate and increased body protein catabolism initiated by the causative injury.

TREATMENT

Treatment is based on the pathologic physiology of the syndrome. Since the renal lesion is reversible and self-limited, the logical approach is to maintain fluid and electrolyte balance during the interval of time when the nephron is not functioning as an excretory unit. Therapy should be aimed at compensation of fluid and electrolyte loss, sparing catabolism of protein, and prevention of ingestion of protein. In the acute syndromes in which no previous renal damage is present, increasing levels of blood nitrogen are not cause for concern. These patients do not die of uremia. They die of disorganization of the fluid and electrolyte balance between the cellular and intercellular spaces. As suggested by Muirhead,[24] Pratt,[25] and Kugel,[26] treatment should be adjusted to the three phases of the syndrome: 1) renal ischemia, 2) renal impairment, and 3) diuresis. As soon as oliguria or anuria is recognized, blood determinations of nonprotein nitrogen, chloride, carbon dioxide combining power, and serum potassium should be obtained. Appropriate fluids and electrolytes may then be given to correct any inequities. Fluids are regulated to make up for insensible losses by perspiration, through the bowel, and through nasogastric suction or vomitus. In infants this amounts to from 30 to 60 cc per kilogram per 24 hours, and even less in older children.[25] Glucose is given in each intravenous infusion to spare protein catabolism and no proteins are given by mouth or parenterally. In the diuretic phase, tubular failure to reabsorb threshold substances from the glomerular filtrate may precipitate a severe hypochloremia. During this phase, adequate fluids and electrolytes must be given to avoid dehydration and hypochloremia. Hypopotassemia must be watched for and treated if it occurs. In children who have had no previous renal disease, such procedures as renal decapsulation,[12, 27, 28] removal of metabolites by such methods as the artificial kidney,[29] peritoneal[30] or intestinal lavage[31] are not indicated until after 10 to 14 days of anuria. In most cases, with proper conservative measures, diuresis will occur between 7 and 14 days without such drastic aids.

The following cases of lower nephron nephrosis resulting from transfusion reaction and sulfonamide reaction were successfully managed by a conservative regimen of fluid and electrolyte managements.

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[24] Muirhead, E. E. and Fromm, C. S.: Severe acute renal insufficiency with recovery. J. A. M. A., 137: 1378-1382, 1948.

[25] Pratt, E. L.: Treatment of anuria. Am. J. Dis. Child., 76: 14-25, 1948.

[26] Kugel, V. H.: Management of acute toxic nephrosis. Am. J. Med., 3: 188-205, 1947.

[27] Abeshouse, B. S.: Renal decapsulation. J. Urol., 53: 27-84, 1945.

[28] Peters, J. T.: Oliguria and anuria due to increased intrarenal pressure. Ann. Int. Med., 23: 221-237, 1945.

[29] Kolff, W. J.: The artificial kidney. J. Mt. Sinai Hosp., 14: 71-79, 1947.

[30] Fine, J. and Seligman, A. M.: Treatment of acute renal failure by peritoneal irrigation. Ann. Surg., 124: 857-878, 1946.

[31] Vermooten, V. and Hare, D. M.: Gastric lavage in treatment of uremia associated with prostatism. J. Urol., 59: 907-919, 1948.

CASE REPORTS

Case 1 (R. M. No. 30447). A 10 year old girl was admitted to the Children's Hospital in July 1949. Her mother had noticed an abdominal mass 1 week previously. Physical findings and pyelographic evidence pointed to a diagnosis of Wilms' tumor. On the afternoon of the second hospital day, a transperitoneal nephrectomy was done. The operation was without incident; her systolic blood pressure was maintained between 110 and 130 mm. of mercury. She received 350 cc citrated whole blood during the procedure and this was followed by a constant, slow, intravenous infusion of 5 per cent glucose in water. On the night of the operation the temperature rose to 104.2F and oliguria was noted. Only 175 cc urine was excreted during the first 48 hours. The urine was smoky in color, contained albumin grade 4 and had a specific gravity of 1.010. Anuria followed this short oliguric phase and lower nephron nephrosis or reflex anuria was suspected. On the day following operation, the plasma chloride content was 530 mg. per cent and the next day, without significant change in the chlorides the nonprotein nitrogen was 134 mg. per cent. On the third postoperative day, it was discovered that the blood given by transfusion at the time of operation was incompatible due to mislabeled blood used in cross matching. As soon as the true diagnosis became apparent, a regimen was set up in which the fluids were limited to replacement of losses through the skin, bowel, and nasogastric suction. The latter was required to control vomiting. Electrolytes were given in the parenteral fluids in amounts to maintain near normal levels, and these needs were determined by daily plasma chloride and carbon dioxide combining power determinations. The nonprotein nitrogen gradually rose to a level of 212 mg. per cent, but edema was minimal. Parenteral amino acids were avoided and glucose was given in each intravenous infusion to spare catabolism of body protein and minimize the release of potassium into the circulating blood plasma. The anuria and severe oliguria persisted for 9 days, at the end of which time diuresis developed. During this phase, care was taken to prevent dehydration and hypochloremia. The patient's condition improved rapidly, gastric suction was discontinued, and oral intake of fluids and food allowed. A low protein diet was used during this phase. A transfusion of citrated whole blood was given during the third week and deep x-ray therapy was started. (A total of 3000 r were given.) The nonprotein nitrogen level approached normal figures when the patient was discharged on the twenty-first postoperative day. Close clinic follow-up has revealed no evidence of metastasis. The nonprotein nitrogen level 3 months after operation was 34 mg. per cent. The hospital course of this patient is shown in figure 1.

The pathologist reported that the tumor measured 20 by 10 by 10 cm. Histologically, the tumor was an adenomyosarcoma with invasion of the kidney.

Case 2. (V. L. No. 13164). A 20 month old female infant was admitted to the Children's Hospital in March 1948, because of recurrent pyuria and bacteriuria.

Culture of the catheterized urine resulted in growth of beta hemolytic streptococcus. The infant weighed 10.4 kilograms. Sulfamerazine (2 gm. daily) was given. On the fifth day, after receiving a total of 8.5 gm., hematuria developed and sulfonamide crystals were found in the urine on microscopic examination. The sulfamerazine was stopped. At this time the blood sulfonamide level was 14 mg. per cent. Anuria developed the next day and lasted for 36 hours. With the anuria, vomiting occurred and lethargy was marked. The nonprotein nitrogen level rose to 144 mg. per cent. Conservative management was carried out and fluids were restricted to basic maintenance needs. Recovery was prompt and uncomplicated. No weight was gained during the period of oliguria and anuria; no edema was noted, and there was no elevation of the blood pressure. Within 3 days after onset of diuresis, the nonprotein nitrogen level had fallen to 82 mg. per cent and 4 days later it was 39 mg. per cent. On subsequent visits to the clinic, urinalyses were within normal limits. The nonprotein nitrogen level was 33 mg. per cent 14 months later. The hospital course is shown in figure 2.

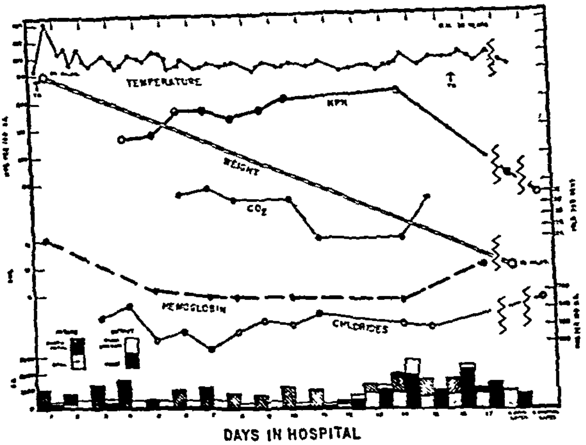

FIG. 1. Case 1. Note relative stability of chloride and carbon dioxide combining power evels.

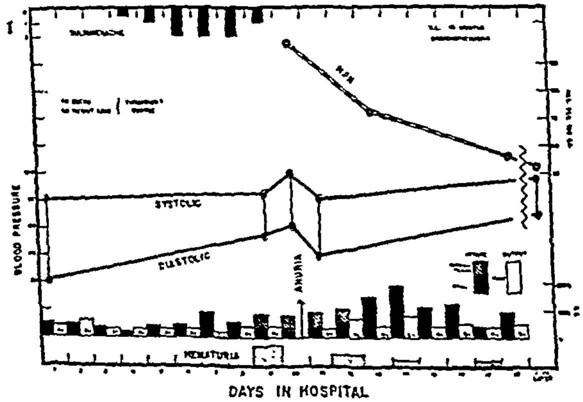

FIG. 2. Case 2. Note increase of blood pressure during oliguria and anuria

COMMENT

In the past, the high mortality rate in cases of lower nephron nephrosis been due largely to a lack of appreciation of the pathologic physiology pres These patients were literally drowned in their own fluids in an ill-advised atte to "dilute toxins" or force diuresis. Most of the pathological reports of f cases mention massive pulmonary and generalized edema.[1, 2, 9] The kidney these cases are physiologically unable to excrete urine until regeneration of tubular epithelium has occurred. Likewise, it seems illogical to use meas such as renal decapsulation when the edema of the kidney can be more rea controlled by proper management of the fluid and electrolyte intake. In th cases that have been reported as responding to decapsulation, the operation been done at a time when tubular epithelial regeneration was about compl so that the diuresis probably was due to the latter rather than to the decapsu tion. The use of various methods of extrarenal dialysis for removal of wa products in the blood have no place in the treatment of this syndrome in child with no previous renal lesion until 10 to 14 days have elapsed. One exception this rule may be an anuria due to a crushing injury in cases in which blood stuc reveal a mounting serum potassium level. Removal of potassium by dialy may help to prevent potassium intoxication and death. Mortality rates in lo nephron syndromes will drop precipitously when the principles of conservat management are properly understood and applied.

SUMMARY

The precipitating factors, clinical picture, blood chemistry aspects, and path logical histology of lower nephron nephrosis are briefly reviewed.

Evidence from the literature suggests that death in cases of this syndrome not due to uremia, but rather to a disorganization of the fluid and electroly balance.

The reversibility of the renal lesion is stressed and treatment, based on t premise that recovery will occur if fluid and electrolyte balance are maintain on a conservative basis until regenerative changes occur in the damaged tubul epithelium, is outlined.

Radical measures such as decapsulation and extrarenal dialysis are not i dicated in cases of children with no previous renal lesion, until the anuria ha persisted longer than ten to fourteen days.

Two illustrative cases of the lower nephron nephrosis syndrome with recove in children are presented.

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PROGRESSIVE SYNERGISTIC GANGRENE OF SKIN FOLLOWING INCISION AND DRAINAGE OF RENAL CORTICAL ABSCESS

WALTER F. WELTON

Synergistic gangrene is a condition which is encountered rather infrequently by the general surgeon, but apparently very rarely indeed by the urologist: only 2 cases have been reported following urological procedures. Both of these developed as complications following suprapubic prostatectomy. The purpose of this communication is to present the first reported case of synergistic gangrene following operation on the kidney. Although this condition occurs infrequently, the spectacular benefits following early diagnosis and proper treatment compel one to bear this process in mind should severe wound infection occur. The progressive nature of this disease makes early operative intervention mandatory, and failure to recognize the condition may result in extensive tissue necrosis and death of the patient. Therefore a brief presentation of the salient features of this pathological process seems justified.

Of the 112 cases of progressive synergistic gangrene collected from the literature by Leonard, one followed a prostatectomy (Dodd); and of the others 46 developed after appendectomy, 36 after thoracotomy, 36 after operation for miscellaneous visceral conditions, and 27 after surgical attack on various parietal lesions. Bassow subsequently described another case which developed after prostatectomy. Thus a total of 2 cases, of some 113 reported, has occurred following urological operations.

This condition was first recognized as a clinical entity by Cullen and Christopher in 1924. Brewer and Meleney in 1926 pointed out that the pathological process results from a symbiosis of hemolytic Staphylococcus aureus present in the hair follicles with a nonhemolytic anaerobic microaerophilic streptococcus found in the intestinal tract and in certain peritoneal exudates. In 1936 Willard reported that when staphylococci and streptococci were isolated from a case of synergistic gangrene and separate inocula of these organisms were made subcutaneously into guinea pigs, the development of small localized abscesses resulted. The combination of these pathogens, however, using half the dose of each, produced a large spreading ulcer of the skin and early death of the animal. In this way Willard confirmed Meleney's findings.

Meleney described the early lesions of chronic progressive postoperative synergistic bacterial gangrene as follows:

"It usually begins to appear about the end of the first or second week after operation, either as an infection of the whole wound or as a localized induration about retention sutures. At first the wound becomes red, swollen, and tender. Within the next few days the wound margins or the stitch holes develop a carbunculoid indurated appearance. The center of activity becomes purplish in color, while the outer zone takes on a brilliant red tint. The whole region becomes

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exquisitely tender. *This symptom is an outstanding feature of the disease.* Within a few days the purplish areas become frankly gangrenous. The color of the dead skin changes to a dirty greyish-brown and the surface is dull, like suede leather."

The appearance of the lesion as described above, with the advancing zone of erythema and accompanied by excruciating pain along the gangrenous edge of the ulceration, is characteristic. The patient is mentally depressed. Septic temperature and chills are absent, however, unless other complications are present. The usual aerobic cultures are not sufficient to confirm the diagnosis; anaerobic cultures from the erythematous zone are necessary.

Meleney classifies this condition as a chronic gangrene. It must be differentiated from the following: 1) The chronic undermining ulcer caused by an anaerobic nonhemolytic streptococcus, which produces a moderately painful lesion with liquefaction of subcutaneous fat, but no gangrene. 2) Fusospirochetal gangrene, a fulminating process which spreads widely and penetrates deeply to destroy even bone. This condition almost always follows a human bite which has implanted in the tissues a mixture of organisms, including anaerobic non-hemolytic streptococci, fusiform bacilli, and spirochetes. 3) Gangrenous amoebic infection of the wound, which may follow incision and drainage of an amoebic liver abscess. In this condition there is frequently a history of amoebic dysentery and amoebae may be found in the exudate and in the stools. 4) Chronic gangrenous impetigo, which is usually caused by hemolytic streptococci and staphylococci. The lesions of this disease begin as vesicles, but there is progression through pustular and gangrenous stages to eventual coalescence. 5) Miscellaneous acute gangrenes due to hemolytic streptococci, gas-forming bacilli, or gangrenous erysipelas.

Treatment of progressive synergistic gangrene by wide excision, using cautery or scalpel, should be carried out as soon as the diagnosis is made. The excision must extend well beyond the red zone of advance which contains the anerobic organisms. Some surgeons believe that if this is done the remainder of the treatment is of little importance, though activated zinc peroxide paste may be applied. Dodd has pointed out the ineffectiveness of many forms of treatment formerly used, such as vaccines, maggots, germicidal pastes and liquids, secondary suturing, and sulfonamides.

CASE REPORT

S. W., (647-1563), a 39 year old white man, was admitted to the Seaside Memorial Hospital on June 24, 1947, complaining of pain in the right flank, chills, fever, and night sweats of 1 week's duration. In December 1946, and in January 1947, he gradually developed anorexia, and lost about 20 pounds in weight. A month later he noticed epigastric and right hypochondrial pain. All studies were negative save for radiographic evidence of a spastic duodenum. Rest and a diet were prescribed, and this regimen resulted in an improvement, of short duration, in his gastric symptoms. However, he soon began to lose more weight and a daily temperature elevation occurred. Three weeks prior to admission he noted moderate, gradually increasing pain in the right flank which was accentuated by palpation of this area. The patient had always been very active, and in good health until the onset of this illness. He had had no previous operations or serious illnesses. There was no history of genito-urinary disturbance of any kind. He had not been in the armed service, but had travelled as a ship's radio operator to Panama and South America from the age of 15 to 21 years. He had spent about 2 months at the age of 18 in Honduras. He gave no history of dysentery. There was no family history of cancer or tuberculosis.

Physical examination revealed an American male of 39 years, of sallow complexion, weighing about 145 pounds, who was apprehensive but fairly comfortable. The heart rate was 90, blood pressure 138/80, respirations 20, and temperature 100.4F. There was tenderness over the right kidney; the liver edge was not palpable. The remainder of the physical examination was normal.

Urinalysis showed a specific gravity of 1.012, pH 5.5; no albumin or sugar was present. On microscopic examination of the sediment only a rare leukocyte was seen, and there were no red blood cells. The hemoglobin was 12.6 gm. per 100 cc; the red blood cell count was 3,500,000; the white blood cell count was 16,550. Differential cell count revealed that 71 per cent were polymorphonuclears, of which 11 were stab forms and 60 were segmented; 27 per cent were lymphocytes, and 2 per cent were monocytes. Blood Wassermann and Kahn tests were negative.

An excretory urogram showed the right kidney to be larger than the left, the enlargement being in the horizontal rather than the vertical plane. Only the inferior calyces showed any diodrast concentration. The ureter was of normal contour and the psoas muscle shadows were sharply defined. The spine was straight. In the upright view there was descent of both kidneys, with no abnormal mobility and no trapping of the dye. The impression obtained from study of these x-rays was that of an intracapsular mass.

At cystoscopy, indigo carmine appeared in good concentration from the left ureter in 5 minutes and from the right in 7 minutes. The bladder was normal. Catheters passed up to the renal pelves without obstruction. Retrograde pyelograms confirmed the impression given by the excretory urograms that an intracapsular mass was present. Based on the clinical studies and the x-ray findings, a diagnosis of cortical abscess of the right kidney was made.

Although immediate operation was advised, the patient elected to continue the course of penicillin therapy which had been instituted on admission. Progress was not satisfactory, sepsis continued, and the patient finally consented to operation on his eighth hospital day. A cortical abscess of the right kidney, about 5 cm. in diameter, and located in the center of the anterior surface, was opened and about 2 ounces of thick yellow pus were evacuated. All pockets were broken down, the kidney was not mobilized, and the cavity was drained with a soft rubber tube and a Penrose drain. The wound was closed in layers with interrupted chromic catgut sutures reinforced with several retention sutures of stainless steel wire. The patient tolerated the procedure very well, and was returned to his room in good condition.

The patient received supportive therapy following operation, and on the third excision would have prevented much tissue destruction, and would have afforded the patient considerable comfort. However, even if the diagnosis of synergistic gangrene had been made earlier, the end result would have been the same in this particular case because of the overwhelming liver infection which was present.

SUMMARY

The first reported case of progressive synergistic gangrene secondary to operation upon the kidney is presented. Criteria for diagnosis are the excruciating tenderness of the wound and the clinical appearance of the lesion with its advancing zone of erythema and the area of necrosis, in conjunction with the isolation of the causative organisms. The possibility of the patient's having a deep focus of suppuration in addition to superficial gangrene, and that the combination of the two may well prove fatal, should always be borne in mind.

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REFERENCES

Bassow, S. H.: Postoperative progressive gangrene of skin following suprapubic prostatectomy. J. Urol., **54**: 46, 1945.

Brewer, G. E. and Meleney, F. L.: Progressive gangrenous infection of the skin and subcutaneous tissues following operation for acute perforative appendicitis. A study in symbiosis. Ann. Surg., **84**: 438, 1926.

Christopher, F.: Severe spreading carbuncular infection of chest wall following rib resection under local anesthesia. S. Clin. North Am., **4**: 795, 1924.

Cullen, T. S.: A progressively enlarging ulcer of the abdominal wall. Surg., Gynec. & Obst., **38**: 579, 1924.

Dodd, H. et al.: Progressive postoperative gangrene of the skin. Arch. Surg., **42**: 988, 1941.

Leonard, D. L.: Progressive gangrene in an operative wound. Arch. Surg., **48**: 457, 1944.

Willard, H. G.: Progressive postoperative chronic gangrene of the abdominal wall. Ann. Surg., **104**: 227, 1936.

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ANGIOMYOLIPOMA OF THE KIDNEY

GLENN S. MORGAN, J. V. STRAUMFJORD AND E. J. HALL

Angiomyolipomas of the kidney[1] are classified among hamartomas. They occasionally occur in cases of tuberous sclerosis syndroma and are classic instances of dysontogenic "tumors." They may also be encountered in the absence of widespread systemic anomalies and neoplasms. "Primary intrarenal lipomas" were described by Robertson and Hand (1941),[2] and, on the basis of the description and photomicrographs, these are apparently the same as angiomyolipomas. They found 12 cases in the literature and reported 2 additional ones. More recently a tumor was described by Heckel and Penick[3] which was predominantly hemangiomatous, but other types of tissue were also present and these tumors were considered to be of the "mixed tumor" group. The authors concluded that mixed tumors include tumors of varying tissue types, but probably of similar histogenesis.

CASE REPORT

A widow, 70 years old, was admitted to Columbia Hospital on April 20, 1949. Two days previously, pain had developed in the upper part of her abdomen and the succeeding two days she had not felt well and had vomited. On the day of admission the patient had severe abdominal pain and chills.

For many years she had had attacks of pain in the upper part of the abdomen, which were considered due to gallbladder disease, although she had been told that she did not have gallstones. In 1930, she had undergone an abdominal operation the reason for which she did not know. On the basis of the information and the findings, however, we considered that it was an appendectomy and uterine suspension. She had also had a low-grade chronic arthritis that was not incapacitating.

When the patient was examined on admission, she appeared to be well nourished. Her temperature was 102F and her blood pressure, 140 mm. of mercury systolic and 70 mm. diastolic. Pronounced tenderness over the gallbladder region and marked rectus muscle spasm were present. The urine was normal except for an occasional erythrocyte and leukocyte. The hemoglobin was 8 gm. per 100 ml. and erythrocytes 3,000,000 per cubic millimeter.

The patient's condition improved in the next 2 weeks and the tenderness subsided. The hemoglobin arose to 13 gm. and the erythrocyte count to 4,500,000. A hard mass was palpable in the upper right abdominal quadrant, rather more lateral than the gallbladder. X-ray studies revealed that the gallbladder was

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[1] Friedman, N. B. and Ash, J. E.: Atlas of Genito-Urinary Pathology. Prepared at the Army Institute of Pathology, Washington, D. C., from material in the registries of the American Urological Association, Washington, D. C., 1946, 215 pp.

[2] Robertson, T. D. and Hand, J. R.: Primary intrarenal lipoma of surgical significance. J. Urol., 56: 458–474, 1941.

[3] Heckel, N. J. and Penick, G. D.: A mixed tumor of the kidney. Lipo-myohemangioma. J. Urol., 59: 572-576, 1948.

excision would have prevented much tissue destruction, and would have afforded the patient considerable comfort. However, even if the diagnosis of synergistic gangrene had been made earlier, the end result would have been the same in this particular case because of the overwhelming liver infection which was present.

SUMMARY

The first reported case of progressive synergistic gangrene secondary to operation upon the kidney is presented. Criteria for diagnosis are the excruciating tenderness of the wound and the clinical appearance of the lesion with its advancing zone of erythema and the area of necrosis, in conjunction with the isolation of the causative organisms. The possibility of the patient's having a deep focus of suppuration in addition to superficial gangrene, and that the combination of the two may well prove fatal, should always be borne in mind.

ACKNOWLEDGMENTS

The assistance and cooperation of the following are gratefully acknowledged: Dr. Calvin Lauer and Dr. Gustavus Bock of the Department of Surgery; Dr. Joseph A. Tutta of the Department of Pathology (who also took the photographs); Dr. E. J. Rowan and Dr. E. F. Kesling (who kindly referred the patient to me); and Dr. Elmer Belt (who served as urological consultant).

REFERENCES

Bassow, S. H.: Postoperative progressive gangrene of skin following suprapubic prostatectomy. J. Urol., **54:** 46, 1945.

Brewer, G. E. and Meleney, F. L.: Progressive gangrenous infection of the skin and subcutaneous tissues following operation for acute perforative appendicitis. A study in symbiosis. Ann. Surg., **84:** 438, 1926.

Christopher, F.: Severe spreading carbuncular infection of chest wall following rib resection under local anesthesia. S. Clin. North Am., **4:** 795, 1924.

Cullen, T. S.: A progressively enlarging ulcer of the abdominal wall. Surg., Gynec. & Obst., **38:** 579, 1924.

Dodd, H. et al.: Progressive postoperative gangrene of the skin. Arch. Surg., **42:** 988, 1941.

Leonard, D. L.: Progressive gangrene in an operative wound. Arch. Surg., **48:** 457, 1944.

Willard, H. G.: Progressive postoperative chronic gangrene of the abdominal wall. Ann. Surg., **104:** 227, 1936.

the renal parenchyma is unchanged, except in the immediate vicinity of the apparent thrombus.

"On further section, in the fat containing the hollowed-out areas, is a whitish, solid, very soft mass measuring 4 cm. in diameter. This blends with the fat and with the hemorrhage. Another section 1 cm. from the margin of the deep crater in the kidney surface revealed a yellowish white mass, continuous with the ragged and dark tissues comprising the margin of the crater and extending outward into the renal parenchyma, almost interrupting it, but leaving a sharp line of demarcation between it and the persistent parenchyma. The pelvis is not involved. The impression is that the soft mass in the kidney and that in the fat are continuous, of the same nature and neoplastic.

"Microscopic examination (fig. 1): Sections from the mass in the crater on the surface of the kidney reveal a thrombus of recent origin, attached at one point to the wall of an artery of muscular type. This artery contains a wide rupture. There is intimal sclerosis with slight calcification. Around the vessel and often attached to it are many elongated cells, apparently smooth muscle, at times lying between adult fat cells. They also surround the goodly number of smaller and very thick-walled vessels of uncertain type lying near the artery. Some of the fat cells are of adult type, others have central nuclei and finely vacuolated cytoplasm, as in fetal or developing fat. The apparent smooth muscle cells often extend outward from the vessels in a peritheliomatous fashion. Blood pigment is present near the ruptured artery. Sections stained for fat disclose some adipose cells of adult type; the adult cells fail to stain for fat. There is slight chronic interstitial inflammation in the compressed kidney adjacent to the mass. Diagnosis: Angiomyolipoma of the right kidney, destroying a segment of the organ and extending into the surrounding fat; aneurysm of a renal artery with thombosis, rupture and extensive hemorrhage into perirenal fat; slight, focal, chronic pyelonephritis."

In the case just described, one wonders whether the tumor is merely a hamartoma or a true new growth consisting in the main of smooth muscle and adult fat. Favoring the latter diagnosis are: 1) the interruption of a segment of the kidney, destroying it completely, 2) extension of the cells beyond the limits of the kidney into the surrounding fat, and 3) the great cellularity of parts of the mass, the most prolific cells appearing to be smooth muscle.

SUMMARY

A rare type of tumor of the kidney, angiomyolipoma, with a case report has been discussed, stressing the diagnostic difficulties encountered both physical and pathological.

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not functioning and that, except for pylorospasm, the gastro-intestinal tract was normal. Urography showed that the "left renal shadow is normal in size, shape and position. There is enlargement of the midportion and lower pole of the right kidney. Prompt excretion occurs from both kidneys. Calyces, pelvis and ureter on the left are normal. The right renal pelvis and mid and lower calyces are deformed and displaced by a mass in the lower pole. There is no obstruction of the ureters."

After consideration of the clinical and roentgenographic findings, a right clampless nephrectomy was performed on May 12, 1949 through a right transverse abdominal incision. The kidney was of unusual shape and size. It had the appearance of two organs connected by an isthmus, one part appearing to consist of a tumor with an aberrant blood supply. It was necessary to tie two large arteries and three veins. The patient's convalescence was uneventful and when she was examined a year later she was in good health.

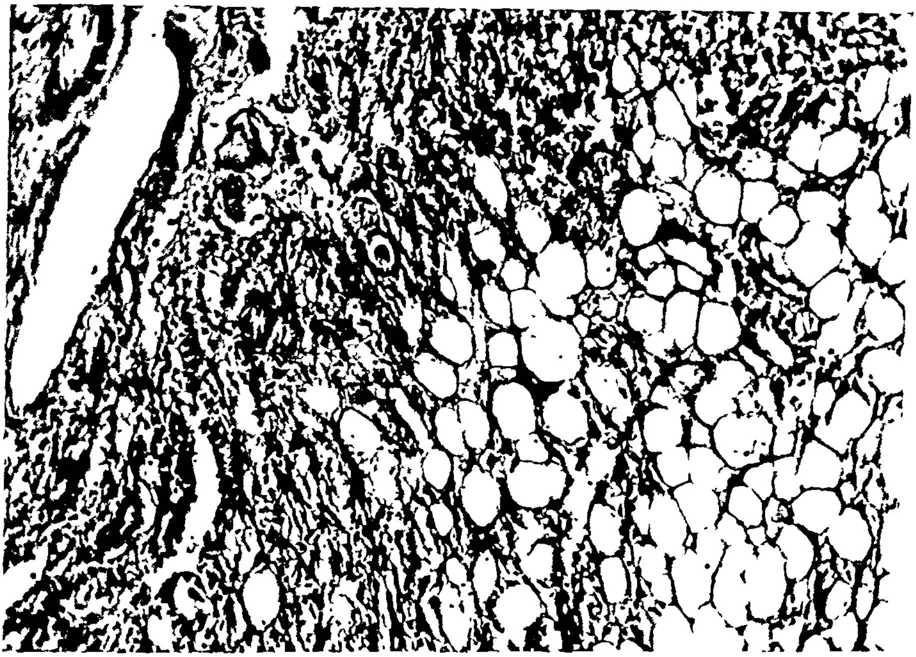

FIG. 1. X-2405-49. Photomicrograph of representative area of renal angiomyolipoma Adipose tissue cells appear as clear, rounded or ovoid spaces. More cellular portions consist *mainly of angio-endothelium in solid sheets, occasionally* opening up to form capillaries. Smooth muscle is not identifiable at this magnification. Elongated, clear spaces at and near left border are blood vessels.

The pathological report on the surgical specimen read as follows: "The kidney stripped of its capsule measured 12 by 6 by 4 cm. On one side is a hollowed-out area 2.5 cm. in diameter, containing blackish scaly material. The surrounding renal tissue is torn and ragged. The clot, adherent to the kidney tissue, lies fairly close to the pelvis, but does not communicate with it. Attached to the kidney is a whitish membrane and some fat in which there are evidence of diffuse hemorrhage and large cavities filled with hemorrhagic material. Grossly, the renal parenchyma is unchanged, except in the immediate vicinity of the apparent thrombus.

"On further section, in the fat containing the hollowed-out areas, is a whitish, solid, very soft mass measuring 4 cm. in diameter. This blends with the fat and with the hemorrhage. Another section 1 cm. from the margin of the deep crater in the kidney surface revealed a yellowish white mass, continuous with the ragged and dark tissues comprising the margin of the crater and extending outward into the renal parenchyma, almost interrupting it, but leaving a sharp line of demarcation between it and the persistent parenchyma. The pelvis is not involved. The impression is that the soft mass in the kidney and that in the fat are continuous, of the same nature and neoplastic.

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BILATERAL LEUKOPLAKIA OF THE RENAL PELVIS

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Leukoplakia of the urinary tract is probably more prevalent than a survey of the literature would indicate. Leukoplakia of the renal pelvis, however, while not so prevalent as that of the urinary bladder, is seen more frequently than leukoplakia of the ureter. Kutzmann, in 1929, collected 67 cases from the literature, and Patch, in a review of 152 cases of leukoplakia of the urinary tract, found it to be present in the renal pelvis and calyces in 36 cases, in the ureter in 6 cases, and in the urinary bladder in 110 cases. It is reasonable to assume that the paucity of cases presenting this lesion in the ureter is, perhaps, because it is not as readily demonstrated at this site by the present means at our disposal.

Leukoplakia of the renal pelvis has been reported, among others, by Beer, Kretschmer, Patch, Low and Coakley, Armstrong et al., Hinman et al., Taylor and Kutzmann. The basic pathology is a squamous metaplasia of the epithelium of the renal pelvis and calyces with keratinization. There is cellular infiltration of the submucosa with varying amounts of edema and fibrosis, depending upon the duration of the infective process with which it is usually associated.

The etiology of the condition is assumed to be chronic infection. Vitamin A deficiency, as demonstrated by Wohlbach and Howe in rats, is a theory which has been promulgated in the past; this, however, has not received as strong support from most investigators. Leukoplakia of the renal pelvis is assumed by most writers to be a pre-cancerous lesion, as is leukoplakia anywhere else in the body.

The symptoms are usually those of chronic urinary tract infection with or without renal colic, and the passage of "gritty flakes" in the urine. It is the passage of these "gritty flakes" in the urine which should lead one to suspect the diagnosis, together with the history of chronic urinary infection and the pyelographic findings.

CASE REPORT

E. P. (L.I.C.H.) 5556, a 47 year old white male radio operator, was admitted to The Long Island College Hospital on June 19, 1949, complaining of passing "gritty flakes" in his urine. Past history revealed two previous hospital admissions for the same complaint. On the last admission, February 1, 1949, retrograde pyelograms revealed a marked, mottled appearing pyelogram on the right side for which a right renal exploratory was advised and which was refused. The patient was then given a course of aureomycin which seemed to benefit him somewhat. Just prior to discharge from the hospital, the patient passed a rather copious amount of gritty material per urethram; this specimen was sent to the pathology laboratory for microscopic examination and reported to be "cornified epithelium." The patient had undergone an epididymectomy at another hospital 7 years previously, the reason for which was unknown to him. He had been treated for prostatitis at various intervals and also stated that he had been passing "gritty flakes" in his urine for 7 years, during some of which time he had served in the Army and had been worked up urologically, the result of this investigation disclosing a small left renal calculus which patient still had on admission.

Physical examination was essentially negative except for absence of the left epididymis. Blood pressure 134/84. The blood chemistry was within normal limits. Hemoglobin 14 gm White blood cells 14,250, neutrophils 86, lymphocytes 14. Kahn and Mazzini tests negative. Urinalysis negative except for moderate numbers of squamous epithelial cells per high power field. Vitamin A oral tolerance test: fasting 15 u., 3 hrs. 65 u., 5 hrs., 200 u., 7 hrs., 130 u. 10 hrs. 60 u. Bladder and right and left kidney urine cultures revealed Staphlococcus aureus.

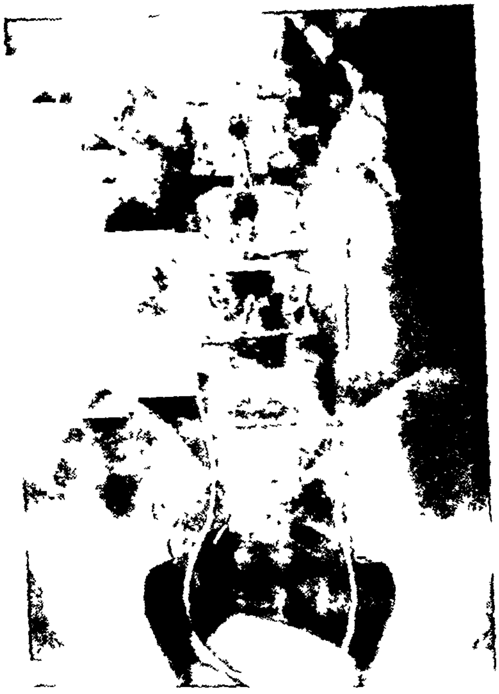

FIG 1

Retrograde pyelograms on June 20, 1949 revealed marked mottling of the pelvis and calyces of the right kidney, together with beginning pyelographic changes of mottling in the left renal pelvis and calyces (fig. 1). The pyelographic findings in the right kidney appeared not to have progressed since previous admission on February 1, 1949. However, the changes apparent in the left pyelogram were not present on previous admission. A diagnosis of bilateral leukoplakia of the renal pelvis with possible neoplasm on the right was made.

Surgical exploration of the right kidney was again advised because it was believed that a neoplasm could not definitely be ruled out. A right renal exploratory was performed on June 21, 1949. The right renal pelvis and calyces were explored and the mucosa appeared thickened, glistening and wrinkled throughout but no gross evidence of neoplasm was present.

A biopsy of the pelvis was taken and a frozen section confirmed the diagnosis of leukoplakia. Nephrectomy was not done. The pathological diagnosis was "chronic pyelitis with squamous metaplasia and hyperkeratosis" (fig. 2).

The postoperative course was uneventful; a low grade fever returned to normal on the fourth postoperative day and remained there for the duration of the patient's hospital stay. The wound healed per primam and the patient was discharged from the hospital on the twelfth postoperative day, July 3, 1949.

The patient has been seen at periodic intervals since discharge and has been more or less asymptomatic, except for one episode of microscopic hematuria and right renal colic associated with the passage of a larger than usual plaque of tissue. His pyuria has improved considerably and, while he still occasionally passes "gritty flakes" in his urine, he does so at less frequent intervals and in much smaller amounts. He has been kept empirically on daily doses of vitamin A, 200,000 u. at first and after 2 months this was reduced to 100,000 u. daily. He is also receiving an acid ash diet and urinary antiseptics. The patient was last seen on January 24, 1950, at which time he was feeling well and working every day, and had been free of symptoms for over a month at that time. The general picture of the patient's condition, however, we know is unimproved even though he feels well at present. The pyelographic findings remain approximately as they were 6 months ago.

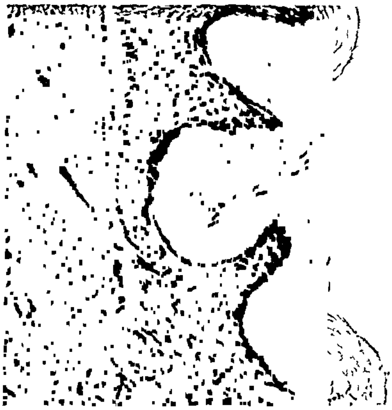

FIG. 2

SUMMARY

A case of leukoplakia of the renal pelvis is presented.

It is presumed that the condition is bilateral because of the history and the pyelographic changes in both renal pelves. Confirmation of the diagnosis was obtained only on the right side, however.

Right nephrectomy was not done because of the presumed bilaterality of the condition. Surgical exploration was performed only to definitely exclude a right pelvic neoplasm.

The "gritty flakes" passed in the urine should be examined by the pathologist for microscopic characteristics of leukoplakia.

Chronic urinary infection, with the passage of "gritty flakes" in the urine, with or without renal colic and retrograde pyelographic changes consistent with this lesion, should lead one to suspect the diagnosis.

The normal vitamin A curve would seem to preclude vitamin A deficiency as a cause of this condition.

We believe the diagnosis can be made preoperatively.

REFERENCES

Armstrong, C. P., Jr., Harlin, H. C. and Fort, C. A.: J. Urol., **63**: 208, 1950.
Beer, E.: Am. J. Med. Sc., **147**: 244, 1914.
Hinman, F., Kutzmann, A. A. and Gibson, T. E.: Surg., Gynec. & Obst., **39**: 472, 1924.
Kretschmer, H. L.: Surg., Gynec. & Obst., **31**: 325, 1920.
Kutzmann, A. A.: Arch. Surg., **19**: 871, 1929.
Low, H. T. and Coakley, H. E.: J. Urol., **60**: 712, 1948.
Patch, F. S.: New Eng. J. Med., **200**: 423, 1929; also J. A. M. A., **136**: 824, 1948.
Taylor, W. N.: Am. J. Surg., **32**: 335, 1936.
Wohlbach, S. B. and Howe, P. R.: J. Exp. Med., **42**: 753, 1925.

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URETERAL CALCULI: EXPERIENCES IN LOOPED CATHETER MANAGEMENT

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The cystoscopic management of ureteral stones is a frequent and sometimes formidable problem. One of the ingenious devices now being used successfully in extracting calculi from this location is the so-called looped catheter. This instrument, as modified and popularized by Ellik, is considered revolutionary in many urological circles.

Having occasion to handle numerous ureteral stone cases in a large Naval Hospital, one of us (L. A. N.) elected to use this type of extractor for the past 2½ years. Those used were home-made and fashioned closely after the pattern recommended by Ellik with two minor exceptions. Less sizable wire was used for the filament, the caliber preferred being that of .005 inches in diameter. Though of less tensile strength and thereby contributing less rigidity to the device, this smaller wire reduced fouling of the dual filament and gave somewhat smoother mechanical performance. In addition the instrument was often stiffened by inserting an ordinary ureteral catheter stylet which the lumen could more easily accommodate because of the reduced size of the steel wire filaments. This extra rigidity seemed of advantage when insinuating the device past a particularly resistant impacted calculus, often at a high ureteral level. Meticulous inspection of and careful repairs to the device lengthened its life and notably enhanced performance.

In general any size or type of cystoscope suffices for the use of this instrument as it is no larger than 5F at any point. The cystoscope is usually removed before traction is instituted. Deliberation at all stages of the procedure has been found distinctly advantageous. As the key to success with such a device dwells upon whether it can be insinuated past the stone, every expedient necessary to accomplish this fact should be at the command of the operator. Not the least important of these are deftness, tactile aptitude and patience. Progress roentgenograms are used liberally by some. Formation of and traction upon the loop continues to conform to previously described techniques.

The ureteral manipulation of such an instrument does not require anesthesia but urethral distress from the cystoscope is nicely avoided by unconsciousness or spinal block. Intradural anesthesia aids ureteral relaxation in trying cases. In this study spinal anesthesia was used thirty times and pentothal sodium just once. Since the latter is known not to aid in relaxation of the tract, its use is purely a favor to an apprehensive patient. In fourteen instances spinal anesthesia permitted successful manipulation after urethral analgesia had failed. However, it should be recorded that four of seven failures under spinal anesthesia later responded with nothing more than urethral instillation of metycaine. This would

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indicate that chance and persistent endeavor play major roles. Most stones were located in the lower third, but thirteen calculi were extracted from the middle third of the ureter and seven were attacked in the upper third. Four stones in this series were actually extracted from the pelvis proper and three of these withdrawn through the full length of the ureter. The fourth one was drawn into the upper ureter where its surgical removal was appreciably facilitated.

The renal pelvis continues to be the more spacious area for closing the loop and from this position the device is usually withdrawn rather quickly to the previously determined level of the stone. This preliminary traction is confined to the pull filament—obviously to keep the loop tightly closed. The initial hang produced indicates contact with the calculus by the caudad tip of the closed snare. Recent experience indicates that no further traction is advisable after this event for the device too frequently slides past the stone without engagement. It is better to allow natural ureteral peristalsis the prerogative of encirclement and fortunately such occurs within a few hours. Formal traction is best instituted following this physiological event. Redundant portions of the instrument may be taped to the abdomen, permitting ambulation and normal micturition during such interim. All traction in this series was limited to the practised hands of trained personnel and no continuously active devices were ever attached for such purpose. Force beyond the recommended four pounds was never used and two pounds or less proved sufficient for most deliveries. The ureteral orifice was the most unyielding of all ureteral levels and greater pull was exerted at this point than at any other. Most deliveries occurred in twenty-four to forty-eight hours, but one stone yielded after seven and one-half days of traction. It was noted that the loop's presence promoted good drainage of urine and practically always eliminated colic. Previous explanations of these two helpful phenomena on the basis of canalizations and splinting seemed quite sound. The actual withdrawal of calculus, though not without some discomfort, was never painful beyond reasonable bounds.

Exceptionally few of the cases presented febrile problems and only in these was chemical or antibiotic therapy instituted. In only one instance was an indwelling ureteral catheter inserted after extraction and in general this was not considered indicated or advisable.

Table 1

Patients with ureteral stone	104
Females	5
Negroes	0
Age group	17–65

Although a compilation of statistics resulting from this particular study points to comparatively brilliant results with the loop extractor, yet, as might be expected, any such instrument manipulated in so distant, minute and fragile a structure could not be expected to be without danger. Spotlighting those instances of structural injury, traceable to either the device or its manipulation, would seem to represent the most profitable part of any such analysis. It is with this goal in mind that the accompanying statistics and pertinent case reports are presented in some detail.

Well over half of the total number of patients had one or more ureteral calculi extracted by means of the loop device.

TABLE 2

Patients subjected to extraction	59
Stones extracted	61
Two stones in a single ureter	1
Stone in each ureter	1
Stones transparent to x-rays	8 (13%)

Forty-five patients were not considered suitable for cystoscopic looped catheter extraction and the mode of treatment instituted was as follows:

TABLE 3

Stones passed spontaneously	17
Stones passed after manipulation	13
Ureterolithotomies	15

Although one patient required six cystoscopies, the over-all average was not excessive. Seldom was traction required for more than two days before the stone was delivered and a force of two pounds or less was usually sufficient. Ureteral meatotomy was necessary for delivery on occasion.

TABLE 4

Cystoscopies per stone	1.6
Average extraction time	48 hrs.
Average traction force	2 lbs.
Maximum traction force	4 lbs.
Maximum traction time	7½ days
Ureteral meatotomies	5

Delivery of extracted stones after leaving the ureter varied somewhat. Slightly more than half were still engaged in the loop when the instrument appeared at the external urinary or urethral meatus. An occasional stone proved the more impressive when its size did not permit delivery from the bladder without preliminary fragmentation. An encircled stone was easier to remove surgically because it was understandably more conspicuous.

TABLE 5

Ureterolithotomies with loop engaged	6
Stones delivered in loop	33
Stones falling into bladder	22
Above stones voided	20
Above stones requiring litholapaxy	2

Results other than desirable which occurred in this series may be listed as follows:

TABLE 6

Ruptured ureters	4
Surgical drainage necessary	3
Nephrectomy necessary	1
Deaths	1

CASE REPORTS

The following four case reports are included to exemplify specifically certain dangers inherent to the device or its handling. All will be found to have resulted from a rupture of the ureter.

Case 1. C. L. R., a white man, aged 32, had a jagged and pointed calculus 1 by 0.6 cm. about 21 cm. above the bladder, in the left ureter. The loop was engaged under spinal anesthesia and traction applied three or four times daily for four days with but 2 cm. progress during that period. Pain in left flank followed traction on fifth day with temperature rising to 101F. A ureterogram demonstrated a ruptured ureter (fig. 1) and ureterolithotomy disclosed a 4 cm. longitudinal tear resulting from the knife-like point of the stone. In spite of surgical drainage and prolonged ureteral intubation, nephrectomy was necessary because of stricture and pyonephrosis.

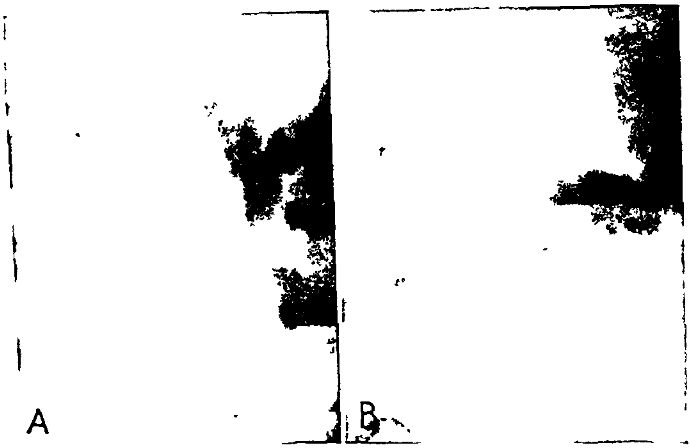

FIG 1. *A*, traction on pointed calculus caused injury to ureter. *B*, injury to ureter demonstrated by ureterogram

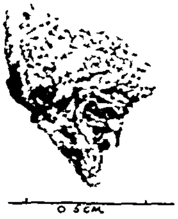

FIG. 1, *C*. Calculus with sharp point

Case 2. R. I. M., a white man, aged 52, had typical left colic without roentgenographic evidence of stone. However, a catheter met obstruction 22 cm. up the left ureter. The loop extractor was used and seemed to stick in the upper ureter where x-ray examination demonstrated malformation of the snare with a spiral or telescopic distortion apparently from fouling of the dual filaments (fig. 2). Filaments were dismantled from the device and removed without difficulty but the patient experienced pain in the left flank. A ureterogram revealed rupture with extravasation. An indwelling ureteral catheter and urinary antiseptics sufficed for uneventful recovery of patient. Soft, mushy, calcareous material was extracted in the loop.

Case 3. D. F. W., a white man, aged 43, had right colic with sufficient new and old history and findings to warrant suspicion of transparent calculus. A looped catheter was used to explore or sweep the ureter for possible stone. The loop closed poorly with the tip not in contact with the side of the device (fig. 3). This was not thought dangerous as usually ureteral tone completes closure. However, traction produced rupture in ureter noted at surgical drainage to be

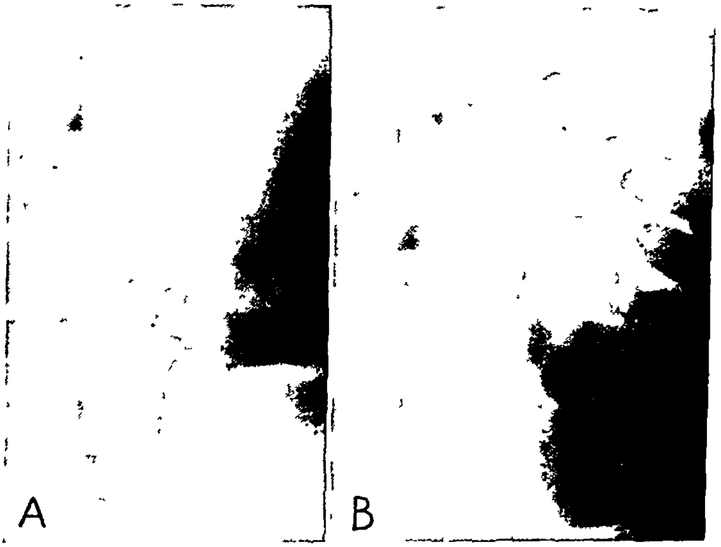

FIG. 2. *A*, telescoped loop resulting from traction on both filaments, caused by fouling of the wires in the catheter. *B*, injury to ureter demonstrated by retrograde pyelogram.

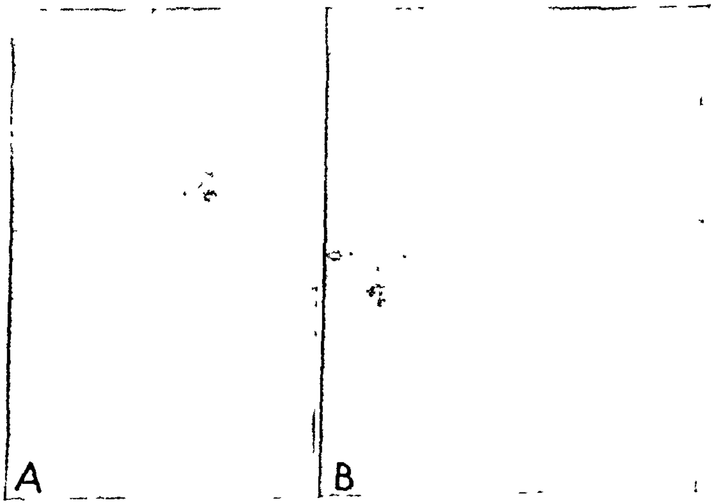

FIG. 3. *A*, incompletely closed loop with long beveled tip. *B*, injury to ureter demonstrated by injecting skiodan through looped catheter.

due to tip of device tearing through for 1 cm. Uneventful recovery after drainage with ureteral intubation. No stone ever demonstrated.

Case 4. E. J. K., a white man, aged 29, had a stone 1 cm. in diameter 8 cm. up the left ureter. The stone was engaged in the loop at the initial attempt but slipped off at traction. Attempt at re-engagement several days later with stylet-reinforced loop extractor resulted in perforation of the ureter well below level of the calculus (fig. 4). Perforation was shown to have been caused by a metal stylet which inadvertently protruded beyond the confines of the device. The patient recovered normally after surgical lithotomy.

These cases illustrate ureteral injury from a variety of reasons during the use of the loop extractor. Basically, one-half were from malperformance of the device; the others were due to faulty judgment or technique on the part of the operator. All could have been avoided and probably would not occur in the hands of an operator aware of such potentialities.

In six instances, loop-engaged calculi were removed surgically for sundry reasons. The presence of this device at the time of operation was consistently advantageous. Three of these are worthy of brief review.

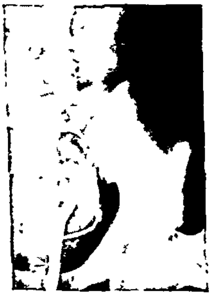

FIG. 4. Perforation of ureter below calculus from a loop catheter stiffened to the end with a catheter stylet.

Case 1. In the case previously described in which a sharp and jagged stone tore through the ureteral wall, surgical removal was performed with the loop device still engaged about the stone. Its presence made the area and stone more conspicuous and aided speedy identification. With the calculus removed, the device was withdrawn through the remainder of the ureter and retained its usefulness in future manipulations.

Case 2. H. M. B., a white man, aged 26, had a stone 1.3 cm. in diameter located in a very small and markedly intrarenal type of pelvis. The stone engaged in the loop and moved 3 cm. down from the ureteropelvic junction into the upper ureter where surgical removal was considered much facilitated (fig. 5). The loop was withdrawn through the remainder of the ureter after the calculus was disengaged.

Case 3. L. A., a white man, aged 26, had one stone 1 by 1.5 cm., located 22 cm. up the right ureter and another on the same side 1 by .5 cm., just 2 cm. from the ureteral orifice. Although the lower stone seemed ideal for extraction, it was believed that the higher one was too large and distantly located for this maneuver. The upper calculus was engaged, however, and made good progress to the sacro-iliac level where it was removed surgically; both its lower position and loop outlined eminence were considered helpful. Interestingly enough this loop was then drawn down the ureter to engage the lower stone which was extracted without benefit of surgery as was originally predicted it should be.

It is believed that the single death in this series might be indirectly attributed to the cystoscopic management of a ureteral stone. H. O. L., a white man aged 51, became ill with chills, fever, pain in upper left abdomen, exquisite tenderness over left kidney region and temperature rising to 104F. Immediate cystoscopy demonstrated a stone of the transparent variety impacted 2 cm. up the left ureter. Initial catheter drainage of foul, purulent, retained urine was followed by loop extractor removal of a nonopaque calculus without incident on the third day. The temperature subsided after extraction only to rise sharply again in a few hours. On the fourth day fever and prostration continued though ureterograms showed no damage. On the fifth day the patient became irrational, and cyanotic, and expired. Necropsy revealed a large infarct of the brain stem in addition to multiple infarcts elsewhere. Although original urine cultures demonstrated Aerobacter aerogenes and streptomycin had been administered, postmortem blood cultures showed Bacillus proteus. In retrospect, better and more prolonged drainage prior to such instrumentation in the face of infection of this magnitude might well have retained life.

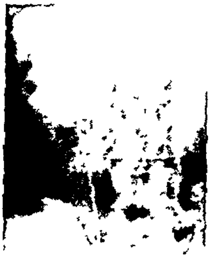

FIG. 5. Calculus too large for loop extraction moved from a small intrarenal pelvis to upper ureter to facilitate surgical removal.

SUMMARY

The loop extractor as used in this study proved to be a valuable device, capable of producing rather impressively brilliant results in the majority of cases. It was quite apparent, however, that either a defective instrument or improper handling of the device might prove dangerous. It is hoped that a frank airing of such exigencies will lead to not only a better understanding of the instrument but also additional faith in its usefulness.

CONCLUSIONS

A critical review of this series of 104 ureteral stone problems would seem to indicate that the loop extractor is a valuable device capable of brilliant performance in an impressively high proportion of suitable cases.

It is quite evident that such a device is not without certain dangers inherent in either imperfections in the instrument or in improper handling. It is also evident that most of these dangers can be avoided.

Prompt surgical removal should be instituted if the engaged calculus does not make normal progress under traction or if acute sepsis develops. Presence of the device aids in surgical identification.

It seems logical to assume that certain mechanical improvements to the instrument such as elimination of one filament and improvement in the mechanics of loop closure would prove highly desirable.

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The opinions contained in this article are those of the authors, and are not to be construed as official, or reflecting the views of the Navy Department or the naval service at large.

REFERENCES

Balkus, V. A.: A looped catheter in the treatment of ureteral calculi. J. Urol., 50: 667–672, 1943.

Ellik, M.: Stones in the ureter: their extraction by looped catheter. J. Urol., 57: 473–478, 1947.

Ellik, M.: The looped catheter ureteral stone extractor: Perplexities in its construction and use. J. Urol., 61: 351–358, 1949.

Wehrbein, H.: Looped catheter. Urol. & Cutan. Rev., 46: 631–633, 1942.

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GLANDULAR TUMORS OF THE BLADDER

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Glandular carcinoma of the urinary bladder is rare. Peacock and Corbett have stated that it comprises only 0.5 per cent of all neoplasms of this organ. Col. J. E. Ash of the Army Institute of Pathology reports that of 2,000 bladder tumors studied only two were adenocarcinoma, and one of these secreted mucus. Howard and Bergman, in 1064 cases, found 8 adenocarcinomas, two of which were of the mucinous type. Culver, Baker, and Larkin found two glandular carcinomas in their series of 531 bladder tumors but failed to state whether either was mucinous. Begg in 1931 collected 44 cases of tumor of the urachus that involved the dome of the bladder and found 19 were colloid adenocarcinoma. Col. R. O. Dart, director of the Army Institute of Pathology, in recent correspondence stated that "only six cases are found in the Bladder Tumor Registry which are felt to be primary glandular type neoplasms arising in the dome of the bladder." Doctors Mostofi and Dean are studying the glandular tumors of the bladder registered with the Army Institute of Pathology and state in a recent letter "... over 100 glandular tumors of the bladder are in the files of the registry ... and we have felt that in every glandular tumor of the bladder it is important to rule out a primary site elsewhere. We have been able to do this in a number of our cases and feel that there is definitely such an entity as primary adenocarcinoma of the bladder (which, of course, is not a new discovery) and that a group of these tumors arise from the urachal region. In a larger number we are in the process of getting follow-up information to rule out the presence of a primary lesion elsewhere." As urologist to the Stadtische Polikinik, Vienna, Austria, Theodor Hryntschak has seen only 1 case of gelatinous adenocarcinoma and this involved the dome of the bladder. From the wealth of material seen at the Pathologisch-Anatomisches Institute Der Universitat Wien, Prof. H. Chiari was able to find only 1 case of colloid adenocarcinoma.

The majority of these tumors have been found in males, most often in the middle or later periods of life. The average age was 46 and the youngest on record was 26. Seventy-five per cent of the cases have expired in less than two years, however, survivals of 5, 7, 9, and 11 years have been reported. There is general agreement upon the importance of the urachus in the origin of these tumors.

EMBRYOLOGY

During embryonal development a wedge of mesenchyme situated between the hind gut and the allantois grows caudalward dividing the primitive cloaca into a ventral urogenital sinus and a dorsal rectum. The bladder is derived from this ventral urogenital sinus while the elongated apex of the bladder which is continuous with the allantois is known as the urachus. In the fetus this structure is patent but in the adult the lumen becomes obliterated and the structure is then known as the middle umbilical ligament, the main function of which is to support the bladder. However, Begg has stated that by thorough histological examination remains of the urachus can be found in two out of three umbilical ligaments.

The lining cells of the urogenital sinus adapt themselves to the specialized function of the bladder and are differentiated into transitional cell epithelium while those lining the urachus have no particular function and remain as primitive cells. This epithelium may be transformed into glandular or squamous epithelium, however, the entodermal influence usually predominates with the production of adenomas or adenocarcinomas.

ORIGIN

While most of the evidence points to the urachus as the origin of the majority of glandular tumors of the bladder, it seems evident that some arise in areas situated remotely from the bladder dome and are definitely not concerned with urachal tissue. The appearance of adenocarcinoma in a structure which is generally considered void of glandular tissue has led to much controversy. The fact that several etiological theories exist is proof enough that the exact origin is still in doubt. The various theories can be grouped into three main categories: 1) anatomical, 2) embryological, and 3) metaplastic.

The first group, the anatomical, is based on the theory that the normal bladder contains glands. These were described by Albarran in 1892 as short, tubular structures situated near the trigone or vesical neck. He spoke of these as paraprostatic glands. Virchow and other German writers spoke of aberrant prostatic glands while Aschoff considered them to be glands of the posterior urethra. However, not all workers agree as to the existence of these structures. Enderlen and Fornuggini found the mucosa of the bladder at birth to be transitional cell epithelium without evidence of glandular formations. Sindoni failed to find any glands in the bladders of 11 children and 9 adults ranging to 60 years of age. Does the normal bladder contain glands? This question still remains unanswered, but if they are present, they could well be one site of origin of adenocarcinoma.

The second theory, the embryological, states that these tumors arise from inclusions of cells from either the urachus or the cloaca. Tubular, gland-like structures at the fundus, in the region of the middle umbilical ligament have been described by Begg, Saphir and Kurland, and others. Saphir and Kurland found evidences of glands in this area in 9 out of 10 cases, and Begg collected 19 cases of colloid carcinoma arising from urachal cell nests in the fundus. Therefore, it has been well established that these inclusions from the urachus give rise to mucinous adenocarcinoma.

The same is not true of the theory that glandular tumors arise from inclusions of cloacal cells. No definite proof exists that nests of cloacal cells can be found in the bladder mucosa. However, the theory states that the cells may persist in the bladder after division of the cloaca, or they are the result of a retrogressive metamorphosis.

The third theory, the metaplastic, states that glandular elements arise in the bladder from transitional cell epithelium following long continued cellular irritation. Von Limbeck in 1887 and Von Brunn in 1893 described gland formations in the bladder wall arising from buds of hyperplastic transitional epithelium which had been elevated into folds or papillae with the formation of large, branching, gland-like crypts. As the hyperplastic tissue builds up on the surface the blind ends of the crypts become detached and are known as the cell nests of Brunn. The central portion of these epithelial nests were thought by Von Brunn to undergo degeneration and thus form the lumen of the glands. Under certain stimuli, the most common being infection, these glands proliferate and become cystic giving rise to cystitis cystica or cystitis glandularis.

Patch and Rhea concluded that as a result of irritation and infection the bladder mucosa undergoes a metaplasia which results in leukoplakia, cell nests of Brunn, cystitis cystica, cystitis glandularis and adenocarcinoma. They consider all of these to be progressive changes of the same process. Some authors believe that cystitis cystica and cystitis glandularis arise from the subtrigonal glands of Albarran but the scarcity of these structures speaks against their being the site of origin. Karsner explained the origin of cystitis cystica as being a result of chronic irritation causing the cells to de-differentiate and resemble embryonal cells. Then, as they grow, there occurs a re-differentiation into a cell entirely dissimilar which bears no resemblance to the original structure. Some authors believe that adenocarcinoma may form from transitional cells directly and not pass through the stages of cystitis cystica or cystitis glandularis. Although this type of bladder tumor has never been observed to occur from cystitis cystica or cystitis glandularis, it has been suspected that as long as glandular structures are known to appear through metaplasia, a carcinomatous change in these glands is not impossible. Ewing considers cystitis cystica a forerunner of carcinoma. Eisendrath and Rolnick state that it is not a long step from cystitis glandularis to one of the forms of carcinoma, and Craig considers cystitis cystica potentially malignant.

The bulk of support for the metaplastic theory is derived from cases of exstrophy of the bladder. Invariably mucus-producing glands that are similar to intestinal glands are found in exstrophic bladders. In these patients the bladder mucosa is under constant irritation from clothing, infection, or devices designed to cope with the spilling of urine and attempts to protect itself by producing glands that secrete a protective layer of mucin. Abeshouse found 21 out of 27 cases of carcinoma in exstrophic bladders were adenocarcinoma. This is a much higher percentage than is found in the normal bladder.

SYMPTOMS

The passing of gelatinous or mucinous material in the urine in adenocarcinoma is really the only symptom that tends to differentiate it from other types of bladder tumor. Silent hematuria is usually first noted. The symptoms of urachal tumors are identical to other bladder tumors except that they occur later in the course of the disease since the bladder mucosa is involved later. Often there are no bladder symptoms and the only finding is a mass in the suprapubic region which produces suprapubic pain or tenderness.

DIAGNOSIS

Cystoscopy usually reveals an ulcerating mass involving the bladder wall which is covered with a gelatinous material that is difficult to scrape from the surface. The diagnosis is finally made by the microscopic appearance of the tumor tissue. In the case of urachal tumors there may or may not be visual evidence of the lesion in the bladder, depending upon the extent of involvment of the bladder wall. Sometimes there is only an impression of a mass pressing the dome, while in other cases papillary fronds or ulcerated areas are seen. Occasionally gelatinous material exudes from the tumor. Cases have been reported where there was no tumor tissue present on the mucosal surface of the bladder but a flow of gelatinous material was seen coming from a small opening in the dome of the bladder. Funnel-shaped retractions of the apex have been reported. When the only finding is a mass in the anterior abdominal wall just above the symphysis, the differential diagnosis is difficult and usually made at the time of operation. An abscess in the space of Retzius may be confused with neoplasms of the urachus, but the history and clinical course tend to differentiate it. Lipoma of the anterior abdominal wall, cysts of the abdominal cavity, and neoplasms of the omphalomesenteric duct are often confused with these tumors.

PATHOLOGY

Structurally, glandular tumors of the bladder resemble adenocarcinoma of the gastro-intestinal tract, especially the rectum. They are composed of multiloculated spaces which are separated by thin septa of fibrous tissue. These spaces contain clear, thick, gelatinous material. The cells that line the spaces are cylindrical, with basal nuclei and often invade the fibrous stroma. The cytoplasm may be replaced by a gelatinous material which pushes the nucleus to the periphery producing signet-ring type cells. Areas of necrosis, calcification and hyalinization may be present. Distant metastases are rare and late but local extension is the rule.

Rectal carcinoma differs from adenocarcinoma of the bladder in that it produces a more permanent or stable cell. In the bladder neoplasms the production of mucin is so rapid that areas of pressure necrosis are found and the cells are killed by their own product.

Most of the urachal neoplastic growths originate in the upper portion of the intramural segment or the lowermost portion of the supravesical segment. When arising in this location, it is most often encapsulated and extends into the space of Retzius between the transversalis fascia and the peritoneum. The majority finally penetrate the bladder mucosa but only after they have attained considerable size. This leads one to believe that they exist as benign tumors for a long period of time and finally develop characteristics of malignancy. Varying in size from 2 to 20 cm. in diameter, they may be cystic, and sometimes become adherent to the peritoneum and involve the abdominal viscera by direct extension.

Those tumors that are situated entirely within the intramural or intramucosal segments of the urachus have no capsule. The acini lie in direct contact with the muscles and the mucosa of the bladder and invade these structures early. They do not attain the size of those in the supravesical segment but produce symptoms much earlier.

TREATMENT

Surgical removal is the treatment of choice whenever the location and the degree of extension of the tumor permit. Distant metastases are rare but local recurrences at the site of operation are the rule. Therefore, excision must be radical. When the base of the bladder is involved, cystectomy with transplantation of the ureters to the skin or bowel may be considered. Few cases are seen sufficiently early to justify this procedure and more palliative measures are resorted to. These consist of endovesical removal, fulguration, resection and implantation of radium. If the tumor involves the dome of the bladder as in the urachal cases, open operative removal may give good results. It involves excision of the umbilicus, a wedge-shaped piece of tissue from the transversalis fascia and the peritoneum, and at least the upper half of the bladder. One must bear in mind that urachal carcinomas are primarily supravesical in origin and, therefore, are not amenable to endovesical therapy.

CASE REPORTS

Case 1. On July 28, 1947, Mr. C. R. W. (No. 67060) aged 65, was admitted to Watts Hospital with hematuria as the chief complaint. On 2 occasions, about 10 days prior to admission, he had passed blood and clots in the urine. There was no pain or any other symptom associated with either of these episodes. He had recently experienced nocturia 2 or 3 times nightly. Urinalysis revealed both pus and blood. Five days prior to admission he noticed a dull, aching pain in the bladder region which radiated into both flanks. There was a sensation of fullness in the rectum after bowel movements. No other symptoms were elicited.

Physical examination revealed an elderly, white man who did not appear acutely ill. The lungs were normal. The heart was enlarged to percussion while the rate and rhythm were normal. There was a soft mitral systolic murmur which was transmitted to the axilla. Blood pressure was 164/90 and the peripheral vessels showed moderate sclerosis. The abdomen was markedly distended but in spite of this the liver was palpable three fingers breadth below the costal margin in the midclavicular line. It was smooth and nontender. A firm suprapubic mass was palpable and thought to be bladder. Rectal examination revealed no enlargement of the prostate but the rectal shelf was hard and fixed, and an annular lesion was palpable in the rectal wall about 2 cm. above the prostate. The initial impression was carcinoma of the rectum. On July 29 a proctosigmoidoscopy was performed; carcinoma involving the rectum was suspected. The pathological report from a biopsy specimen confirmed this opinion.

On July 30, after removal of many blood clots from the bladder, cystoscopy showed an irregularity at the vault of the bladder within the air bubble. The exact nature of this abnormality could not be determined. On August 2 the abdomen became distended and a Wangensteen tube with suction was used. On passing a rectal tube a great deal of liquid feces and gas escaped. On August 11 the patient suddenly developed severe dyspnea, cyanosis, and pain in the chest. He remained seriously ill for 2 days and then improved slightly. An electrocardiogram indicated a hypertensive heart with possible coronary occlusion. On August 18 the patient became semicomatose and expired the following day. The immediate cause of death was assumed to be coronary occlusion.

The autopsy performed by Dr. J. U. Gunter confirmed this assumption. An infarct was found in the wall of the left ventricle produced by occlusion of the descending branch of the left coronary artery. Other findings were chronic, passive congestion of the liver and miliary lung abscesses. In the fundus of the bladder there was an elevated, nonulcerated, disc-shaped plaque measuring 2 by 2 cm. (fig. 1, *A*). The pelvic floor and cul-de-sac were heavily infiltrated with a greyish-white tumor that involved the posterior wall of the bladder, seminal vesicles, right ureter, and rectum. Enlargement of the pelvic and aortic lymph nodes was noted. The gastro-intestinal tract was heavily infiltrated with tumor throughout most of its length. There was a tumor mass proximal to the pylorus on the superior border of the stomach measuring 2.5 cm. in diameter. It involved the gastric musculature but not the mucosa. The duodenum was normal, but the remainder of the small intestine showed heavy infiltration of the mesenteric border with the mestatic tumor. Where the large intestines had a mesentery, a similar process was found. The rectum was involved in the tumor mass of the

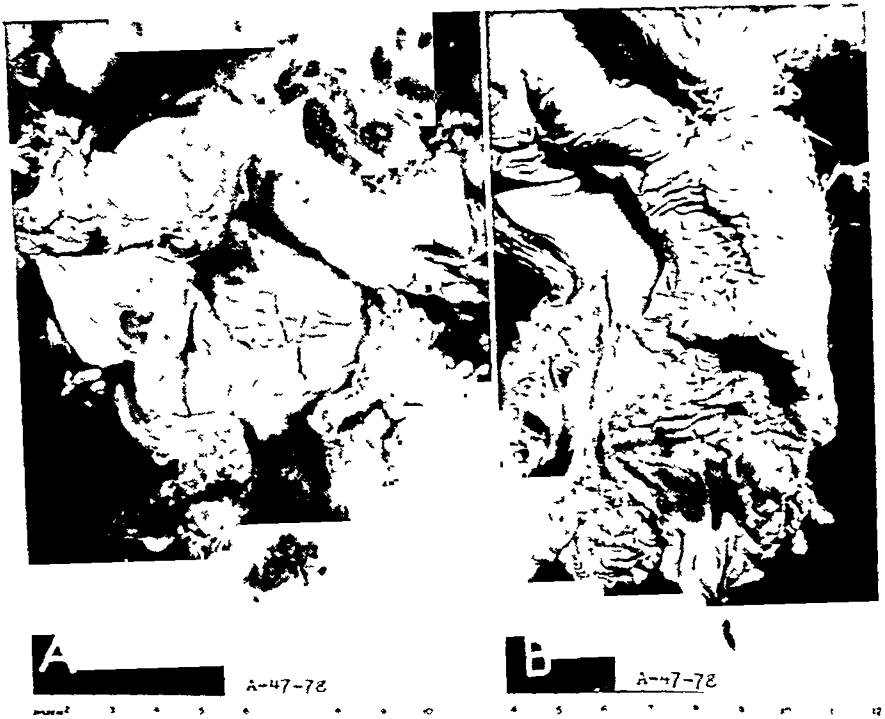

FIG 1 *A*, post mortem specimen showing tumor involving dome of bladder. *B*, gross specimen of rectum and tumor mass of cul-de-sac.

cul-de-sac which obstructed the lumen 2 cm. above the prostate for a distance of 6 cm. (fig. 1, *B*). At no spot in the gastro-intestinal tract was there a break in the mucosa. The tumor seemed to involve only the submucosa and the muscularis.

The microscopic examination of the tissue removed at autopsy was reported as follows: "Bladder . . . . The cells of this tumor are quite pleomorphic. Many of the cells have large, rather pale staining nuclei with an extremely variable amount of fine, dust-like chromatin. The cytoplasm takes the eosin stain and contains vacuoles. Some of the cells contain many small vacuoles which gave the cytoplasm a foamy appearance. Others have a single large vacuole which distends the cytoplasm and pushes the nucleus to one side giving a *'signet-ring'* appearance. Many of the cells have more than one nucleus, frequently as many as five. The stroma of the tumor is a thin net-work of fine connective tissue fibers that separate the cells into small clusters and long strands. The cells are seen infiltrating everywhere between the muscle fibers of the bladder. There are a few areas of dense, round cell infiltration. At one area the tumor cells appear less pleomorphic and more mature. These cells show some attempt at early gland formation." See figure 2, *A*.

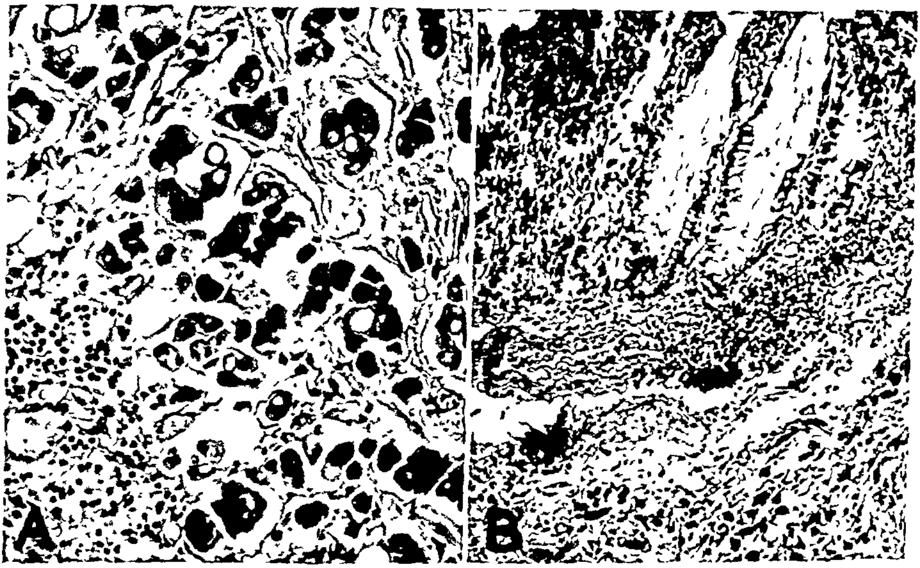

FIG. 2 *A*, photomicrograph of tumor involving dome of bladder *B*, photomicrograph of metastatic tumor of rectum.

Several sections of the gastro-intestinal tract showed the picture of tumor growth involving principally the submucosa and heavily infiltrating the outer muscular coats, but leaving the mucosa intact. Many of the tumor cells were in the lymphatic channels. See figure 2, *B*. Other areas of metastasis were found in the gallbladder, ureter, lung, and pelvic and aortic lymph nodes. The peritoneal fluid contained cells identical to those described in the bladder.

The final diagnosis was mucinous adenocarcinoma of the bladder arising from the urachus.

Case 2. On February 21, 1948, Mrs. M. H. F., aged 64, was seen in the emergency room for renal colic. Several weeks prior to the onset of the pain she had painless hematuria. On physical examination a calculus was found lodged at the urethral meatus. The calculus was removed and the patient immediately voided 300 cc clear urine. She was seen next on April 19, 1949 and admitted to the hospital complaining of hematuria, burning, and frequency of urination. During the interval since her last visit she had had frequent episodes of hematuria with bladder symptoms and at these times she was treated by her family physician. The attacks lasted 2 to 3 days.

On physical examination the patient appeared chronically ill. The skin had a pasty yellow color. The heart and lungs were normal. Blood pressure was 148/76. The abdominal examination was negative except for suprapubic tenderness. A vaginal examination revealed an indurated nodular mass involving the tissues beneath the anterior wall of the vagina and filling both vaults and the cul-de-sac. There had been no bleeding since menopause.

Cystoscopic examination showed the urine to be bloody and clots were evacuated from the bladder. A sloughing, bleeding tumor mass was found involving the entire bladder base. The remainder of the bladder appeared normal but the ureteral orifices were involved in the lesion and could not be found.

Tissue taken by biopsy was examined by Dr. J. U. Gunter and reported as follows: "The tissue contains a tumor the cells of which show wide variation in size and shape. Many irregular cells are seen that are large and hyperchromic. Others contain one or more large vacuoles. The cells are arranged in large clusters and cords and there is little tendency to gland formation. Mitotic figures are numerous." The diagnosis was colloid carcinoma.

Because of the location and extent of the tumor and the patient's poor general condition, no operative procedures were advised, but x-ray therapy was instituted. After 4 weeks of radiation, during which time the patient's condition became worse, she was re-admitted to the hospital. Examination by barium enema showed no lesion in the rectum or colon. During this admission the patient passed for the first time a large amount of gelatinous material in her urine.

One month later the patient returned to the hospital with a spiking temperature and increased dysuria. The blood urea and blood creatinine mounted in spite of supportive therapy and she finally became unconscious and expired in uremia.

A post mortem examination was performed and the gross pathological findings were limited to the urinary tract. The bladder wall was thickened and indurated. On opening the bladder a large, fungating mass was found involving the trigone and right ureteral orifice. The tumor was 4 by 2 cm. in diameter and elevated 2 cm. above the mucosa. The surface was necrotic and friable, but beneath this the lesion was firm. A similar but smaller lesion was seen above the left ureteral orifice. There were numerous small areas of submucosal hemorrhage. The tumor invaded deeply into the thickened bladder musculature but did not extend beyond.

The tumor masses produced an occlusion of both ureteral orifices and resulted in bilateral hydro-ureter. The left ureter measured 0.8 cm. and the right 1.2 cm. in diameter; both were filled with clear urine.

The left kidney was small, weighing 90 gm. and showed no remarkable pathological changes. The right kidney was larger, weighing 165 gm. It showed advanced hydronephrosis with acute pyelonephritis and multiple small abscesses in the cortex.

Report of the microscopic examination of the tissues removed at autopsy was as follows: "The bladder is thick walled and shows hypertrophy of the smooth muscle bundles. Nearly all sections through the bladder show invasion of the wall by tumor. The tumor consists of cords and strands of polygonal cells which show marked variation in size and shape in a stroma of dense connective tissue. Some of the cells are large, giant cells with many nuclei. The nuclei show no uniformity and are hyperchromatic. There are some attempts at gland formation by the tumor cells. In the lumen of the glandular structures there are clear spaces which were apparently filled by a colloid deposit. Mitotic figures are seen and the superficial portions of the tumor show marked necrosis and in some areas calcification."

Sections of both kidneys revealed destruction of the parenchyma by abscesses and areas of inflammatory infiltration.

The final diagnosis was adenocarcinoma of the urinary bladder which by its location produced obstruction resulting in bilaterally infected hydro-ureter and hydronephrosis.

SUMMARY AND CONCLUSIONS

We have briefly discussed adenocarcinoma of the bladder and reported 2 cases. The first is an example of adenocarcinoma arising from inclusions of urachal cell nests in the dome of the bladder. This case is of unusual interest because of the extensive involvment of the gastro-intestinal tract. Since there was no evidence of mucosal involvment, we considered the neoplastic process in the gastro-intestinal tract to be entirely metastatic. Serial sections of the entire tract were not performed, but there was no gross evidence of a break in the mucosa and each tumor mass microscopically revealed an intact mucosa.

The second case is an example of adenocarcinoma involving the base of the bladder, the origin of which is not clear. However, if glands exist normally in the base of the bladder, they could well have been the site of origin of this tumor. It is entirely possible that this neoplasm arose from a metaplastic process since there was at least a 2 year history of bladder irritation and infection.

The three theories of etiology are discussed and the symptoms and diagnosis elaborated upon. These tumors closely resemble those of the gastro-intestinal tract and microscopic differentiation is often difficult. The treatment is surgical removal when possible, supplemented with radiation, and in inoperable cases, radiation alone.

ADDENDUM

While our paper was in the process of publication, a third case of glandular tumor of the bladder came under our observation and the following is a brief abstract of the record.

A. L., No. 72683, a white woman aged 72, was seen September 1, 1950 complaining of urinary frequency and pyuria. She had experienced such episodes with the passage of "soft stones" for many years. X-ray showed no evidence of stone at present. Cystoscopy revealed a necrotic mass above and medial to right ureteral orifice. Under spinal anesthesia, transurethral resection of the mass was done and the base fulgurated. No evidence was found of primary tumor elsewhere in the body, although exhaustive studies were not done. The biopsy report was: "The section displays a papillary configuration of the mucosa with cores of loose, connective tissue covered by moderately well differentiated, neoplastic columnar epithelium, some of which is mucous secreting. Different areas display cells of varying nuclear chromaticity and size. Neoplastic granular structures invade the thickened submucosa. Lymphocytes and plasma cells are scattered throughout the tissue which includes a small amount of muscularis into which the neoplasm does not extend." Diagnosis: Adenocarcinoma of bladder.

REFERENCES

Abeshouse, B. S.: J. Urol., 49: 259-289, 1943.
Ash, J. E.: Urol. & Cutan. Rev., 43: 705-709, 1939.
Begg, R. C.: Brit. J. Surg., 27: 769, 1936.
Begg, R. C.: Brit. J. Surg., 181: 422, 1930-31.
Chiari, H.: Personal communication to the authors, 1949.
Connell, E. J. and Gnassi, A. M.: Am. J. Surg., 47: 157, 1940.
Craig, L. G.: J. Urol., 42: 1197, 1939.
Dart, R. O.: Personal communication to the authors, 1948.
DeWaard, R.: J. Urol., 42: 554, 1939.
Eisendrath, D. N. and Rolnick, H. C.: Urology. Philadelphia: J. B. Lippincott Co., 1943, 4th ed.
Emmett, J. L. and McDonald, J. R.: J. Urol., 48: 257, 1942.
Ewing, J.: Neoplastic Diseases. Philadelphia: W. B. Saunders Co., 1942, 4th ed.
Ferrier, P. A., Craig, L. G. and Foord, A. G.: Urol. & Cutan. Rev., 40: 457-464, 1936.
Fleischman, A. G. and Mauritz, E. L.: J. Urol., 47: 658-663, 1942.
Garvin, E.: J. Urol., 42: 462, 1939.
Hamm, F. C.: J. Urol., 42: 227, 1939.
Hayes, J. J. and Segal, A.: J. Urol., 53: 659-669, 1945.
Howard, A. H. and Bergman, R. T.: J. Urol., 59: 455, 1948.
Hryntschak, T.: Personal communication to the authors, 1949.
Hughes, P. B. and LaTowsky, L. W.: Am. J. Surg., 58: 422-425, 1942.
Karsner, H. T.: Human Pathology. Philadelphia: J. B. Lippincott Co.
Kretschmer, H. L.: J. Urol., 61: 754-765, 1949.
Laughlin, V. C. and Bilotta, J. L.: J. Urol., 42: 358, 1939.
Lowery, S. R.: J. Urol., 42: 118, 1939.
Lowsley, O. S. and Kirwin, T. J.: Clinical Urology. Baltimore: The Williams & Wilkins Co., 1944, p. 1059.
Mostofi, F. K.: Personal communication to the authors, 1949.
Patch, F. S.: J. A. M. A., 136: 824, 1948.
Patch, F. S. and Pritchard, J. E.: J. Urol., 57: 126, 1947.
Peacock, A. and Corbett, D. G.: Northwest Med. Jour., 29: 208, 1930.
Rappopart, A. E. and Nixon, C. E.: Arch. Path., 41: 388-397, 1946.
Saphir, O. and Kurland, S. K.: Urol. & Cutan. Rev., 43: 709, 1939.

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PREPARATION, OPERATIVE TECHNIQUE AND POSTOPERATIVE MANAGEMENT OF URETERO-INTESTINAL ANASTOMOSIS

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Since Thomas Smith of England carried out transplantation of the ureters into the large bowel, in 1878, various operative procedures have been grouped under the general name of uretero-intestinal anastomosis, or implantation. These procedures have received wide publicity and have been performed for additional indications, with clinical results that have established this operation as a sound practice.

The purpose of transplantation of the ureters into the bowel is to secure an exit for the urine, subject to control by the anal sphincter, in patients who because of congenital anomaly, accident, or disease, are unable to void by the natural route. The earliest indication was exstrophy of the bladder. In later years, diversion of the urine from the bladder was undertaken because of intractable vesicovaginal fistula, disuse or removal of the bladder as in vesical malignancy, tuberculous cystitis, interstitial cystitis (Hunner ulcer), and traumatic injury to the bladder and urethra.

Maydl, in Germany, made the first successful intraperitoneal transplantation of the trigone, with intact ureters into the sigmoid, thus preserving the sphincteric action of the ureteral orifices in the hope of preventing ascending infection. Bergenhem, in Sweden, first utilized the principle of extraperitoneal transplantation into the rectum of each ureter, with a rosette of bladder wall about each orifice. It was not until 1911, when Coffey presented the first of his three techniques, that any satisfactory means of solving this vexing problem became available. Others have from time to time offered variations and adaptations, but the fundamental principles of Coffey's techniques are utilized by most surgeons performing uretero-intestinal implantations. In 1948, Nesbit and Cordonnier separately described techniques of direct mucosal anastomosis between ureter and bowel with the elimination of the submucous tunnel. It is their belief that the method avoids obstruction at the site of the operation, and eliminates the associated sequelae. Fundamentally, this method was described by Chalot in 1896, who experimented on dogs, but the procedure was considered impractical and abandoned.

However, the versatility in performing surgery upon the large bowel has increased with the modern therapeutic discoveries, and has resulted in the revaluation of these techniques previously tried and discarded.

The preparation for uretero-intestinal anastomosis is to promote the general nutrition of the patient, and to prepare the bowel for the procedure. The patient is given sulfathaladine, sulfasuxidine or aureomycin 5 times daily; a saline cathartic; a daily enema; vitamin B complex; and a low residue high protein diet for 5 days preceding surgery. A large de Pezzer catheter or a soft colon tube

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is placed in the rectum on the morning of surgery, and maintained in place from 5 to 7 days.

The many surgical techniques of uretero-intestinal anastomosis are too voluminous to describe; therefore, I shall confine my remarks to the Nesbit method used in my last 37 cases. The procedure consists of an end to side anastomosis between the ureter and sigmoid. The parietal peritoneum is incised over the pelvic ureter, and the ureter divided. The proximal end is split longitudinally for a distance of 1 cm. in a normal duct, and longer in the dilated ureter. A redundant loop of sigmoid colon is selected, and the area to be incised is anchored with two No. 40 cotton sutures. A longitudinal incision of equal length to the split ureter is made through all coats of the bowel. The longitudinal bands are disregarded at the site of the anastomosis. Trauma of the bowel is avoided by eliminating the clamping and tying of small bleeders. The ureter and intestine are approximated with a continuous single layer of 00000 chromic catgut. All coats of both structures must be penetrated. Suturing is begun at the proximal end of the split ureter, and meticulous care is used to approximate the edges of the ureter and the bowel. After the anastomosis has been completed, the lateral margin of the incised parietal peritoneum is brought over the anastomosis and sutured to the bowel. This procedure serves to fix the bowel in a position which will preclude any angulation or tension on the ureter, and places the anastomosis extraperitoneally. The left ureter is similarly dissected from its retroperitoneal position, and the same procedure is carried out on the left side as described on the right. The ureter can be brought directly through the mesentery or below the transverse portion of the sigmoid. When cystectomy is not done, the abdominal wound is closed without drainage.

There was a complete duplication of the left ureter in one of my patients. The usual procedure was followed, except that the left ureters were separated a distance of three centimeters, and transplanted one inch apart.

Postoperative management of uretero-intestinal anastomosis consists of nothing by mouth until good bowel activity is established, usually from 3 to 4 days. The fluid intake is maintained intravenously. It has not been my practice to use the indwelling Miller-Abbott tube postoperatively, as ileus and abdominal distention are seldom contributing factors. The rectal tube is removed on the fifth to seventh day, depending upon the condition of the patient. A low residue high protein liquid diet is followed when the patient can take food. An adequate caloric intake is an important factor postoperatively. Penicillin and dihydrostreptomycin are administered daily for 1 week. Blood transfusions are given to maintain the blood count at a normal level during the entire convalescence.

The most interesting phase of the postoperative course and care of these patients is the disturbed electrolyte balance of the blood. The mechanism by which acidosis and alkalosis develops in these patients is still not clear.

Many of the patients exhibit some degree of acidosis characterized by nausea, vomiting, anorexia, shortness of breath, fatigue, weakness and loss of weight. The values of blood urea and plasma chlorides are elevated and the carbon dioxide combining power of the plasma is lowered. Apparently the abnormal acid-base balance develops because of reabsorption of urine, as it occasionally follows the removal of the rectal tube, and is relieved upon replacement of the tube and lavage of the bowel with tap water. When the electrolyte loss is severe $\frac{1}{6}$ molar r. lactate solution 1000 cc, once or twice daily produces prompt relief.

Again when an attempt is made to prevent acidosis by the administration of sodium bicarbonate or sodium citrate supplemented with a low chloride diet, occasionally an alkalosis appears which peculiarly gives rise to similar symptoms.

Although the primary high mortality from leakage, and the frequent severe attacks of pyelonephritis after uretero-intestinal anastomosis have been virtually eliminated, there remains a significantly high morbidity from the disturbed electrolyte pattern of the blood.

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REFERENCES

Bergenhem, B.: Ectopia vesical; adenoma destruans vesicae; extirpation of bladder, implantation of ureters into rectum. Eira (Stockholm), **15**: 268, 1895.

Chalot: La transplantation systematique des deux ureteres et la ligature preventive des deuz arteres ialiaques internes pour extirpation large du cancer diffus de l'uterus par l'abdomen. Arch. de gyn. et de tocol., **2**: 38, 1896.

Coffey, R. C.: Physiologic implantation of the severed ureter or common bile duct into the intestine. J. A. M. A., **56**: 397, 1911.

Cordonnier, J. J.: Ureterosigmoid anastomosis. Surg. Gynec. & Obst., **88**: 441, 1949.

Cordonnier, J. J.: Ureterosigmoid anastomosis. J. Urol., **63**: 276, 1950.

Ferris, D. O. and Odel, H. M.: Electrolyte pattern of the blood after bilateral ureterosigmoidostomy. J. A. M. A., **142**: 634, 1950.

Flocks, R. H.: Management of patients undergoing uretero-intestinal anastomosis. J. A. M. A., **139**: 626, 1949.

Graves, R. C. and Buddington, W. T.: Ureterointestinal anastomosis. J. Urol., **63**: 275, 1950.

Maydl, K.: Ueber die radikaltherapie der blasenktopie. Wien. med. Wchnschr., **44**: 25, 1894.

Nesbit, R. M.: Ureterosigmoid anastomosis by direct elliptical connection. Univ. Hosp. Bull., Univ. Michigan, **14**: 45, 1948.

Nesbit, R. M.: Ureterosigmoid anastomosis by direct elliptical connection. N. Y. State J. M., **49**: 2933, 1949.

Ravdin, I. S. and Walker, J.: Fluid and electrolyte balance. S. Clin. North America, **29**: 1583, 1949.

Smith, T.: Account of an unsuccessful attempt to treat extroversion of the bladder by a new operation. St. Bartholomew's Hosp. Rpts., **15**: 29, 1879.

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CYSTECTOMY AND URINARY DIVERSION IN CARCINOMA OF BLADDER

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The data which will appear in this paper were obtained from our examination and treatment of 230 carcinomas of the bladder observed at the Wadsworth General Hospital during the 6 year period of 1942 to 1947; and from other additional 95 patients suffering with cancer of the bladder observed between 1947 and 1949.

During the period of 1942 to 1947 the Wadsworth General Hospital was a Tumor Center for the States of California, New Mexico and Arizona. Other tumor centers have now been established in other locations in these states.

At the Birmingham Hospital, Van Nuys, 48 patients suffering with cancer of the bladder were examined during 3 years.

Our experience in the use of cystectomy as a surgical treatment for cancer of the bladder was obtained from the treatment of 24 patients at the Wadsworth Hospital, and from 12 patients at the Birmingham Hospital. All members of the consulting staff of the departments of urology, in both hospitals, participated in the treatment of the patients who submitted to cystectomy and diversion of the urinary stream. Most of our remarks will be those concerning our experience with the surgical operation of cystectomy. However, since this is a bilateral problem the first part of which is the complete removal of the urinary bladder and cancer it contains, and the second is maintenance of adequate renal function, both conditions must be considered together; when the bladder is removed there must be some other place to divert the urinary stream through the ureters.

RADICAL SURGERY

In spite of the popularity of the use of diathermy and other more potent electrical currents that may be applied transurethrally in a water medium to desiccate and to resect tumors of the urinary bladder, a distinct tendency exists to broaden the field of cancer surgery to combat malignant disease in this organ with more radical and extensive surgery. These are aimed at cure and are not just an operation that removes part of the cancer, and that leaves other parts in the organ where it originated or in the adjoining structures and tissues.

All urologists who have been practicing this specialty for 20 years or more recognize that the total removal of the bladder has known a slow evolution. Dr.

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Roger C. Graves, who has recently written about this subject, recognizes three distinct phases in its development. The first began in 1887, when Bardenhauer was first credited with performing the first cystectomy. Shortly thereafter, Zuckerkandl collected 64 reports from the literature and estimated the general mortality from this group of cases to be 50 per cent. Dr. Hugh H. Young in *Young's Practice of Urology*, published in 1926, wrote that this operation was wholly unjustifiable. (The disposal of the ureters seems to be the principal problem.) Papin reported his results with bowel transplantation of the ureters in which there was a mortality of 59.2 per cent. In 1935 Dr. Edwin Beer of New York published a book on *Tumors of the Urinary Bladder.* He had better success than the previous surgeons because he implanted the ureters into the skin of the iliac region, and afterward removed the entire bladder.

In view of the mortality it is not surprising that total cystectomy was long regarded with general disfavor. There was little interest in this operation of uncertain outcome and doubtful benefit. We share the opinion expressed by Dr. Roger Graves that the poor result causing this attitude towards total cystectomy was due to inadequate pre- and postoperative care, poor surgical technique and especially to improper selection of cases. Cystectomy was used as a desperate last resort for those patients whose disease had progressed beyond the reach of ordinary forms of therapy and too often beyond the reach of any. We have had to learn from this experience that neither surgery or any other aid will cure advanced, widely disseminated carcinoma of the bladder.

During the last 20 years we have seen the second phase in the development of total cystectomy for cancer of the urinary bladder. This operation has been accepted as a necessary surgical procedure and is being performed with increasing frequency and with some encouraging results. The good results are due to improved surgical technique, adequate control of infection, more adequate pre- and postoperative care, and to wiser selection of cases based on more accurate preoperative diagnoses. This development was slowed down and sabotaged by our attempts to cure carcinoma of the bladder by transurethral methods that permitted desiccation and destruction of tumors in a water medium without opening the bladder. This method failed because of incomplete and incorrect diagnoses made only from cystoscopic observation and the data obtained from the pathological examination of biopsy specimens taken from any one place of the tumor.

The third phase in the evolution of cystectomy for bladder carcinoma is quite recent. Dr. Graves, together with many other surgeons, now includes a radical dissection for removal of the local and regional lymph nodes and lymphatic vessels. This additional operative procedure is becoming an essential and routine part of cystectomy. Until recently the importance of the extirpation of the regional lymph nodes with the removal of the entire bladder has been overlooked. As yet we have had limited experience in the complete removal of all of the nodes in the pelvis along the large vessels and the lower portion of the abdomen, at the same time that the bladder is removed for carcinoma. We have examined the bladders and specimens of the gland bearing tissue and nodes removed surgically and at autopsy trying to learn when and how cancer cells metastasize from malignant tumors of the urinary bladder. We obtained some information about the transfer of cells from a cancer in the bladder to other structures in the body. We cannot see how or why the removal of the lymphatic nodes and lymphatic vessels alone will remove all of the cancer present and prevent further metastasis or have any influence on those already present if adjoining nodes are involved. Distant ones, not in the field of the contemplated operation may be involved as well. It is possible that by taking away the local nodes and gland bearing tissues adjacent to the tumor of the bladder that you may remove all of the cancer, although to us this seems problematical.

During the last 6 months, with the help of the general surgeons, we have completely removed all the organs and tissues from the male pelvis for cancer that began in the prostate gland and involved the bladder and the rectum, and in two other cases in which the cancer had invaded the bladder probably from the bowel. This operation is somewhat similar to the Wertheim operation in the female for the removal of all of the structures in the female pelvis or the so-called Brunschwig pelvic evisceration in the male.

Grade 3 and 4 cancers of the bladder involving all the coats of this structure that have become adherent to the surrounding tissues is not the type of case in which the surgeon can be sure that all of the cancer tissue can be removed by any type of dissection of the glands or by evisceration of all of the pelvic structures. If a bladder malignancy is surgically removed, containing a small tumor that is graded 1 or 2, together with all the gland bearing tissues and then no evidence of cancer is found in any of the nodes or elsewhere in the specimen, we may assume that a complete removal of all of the cancer has been accomplished. When any nodes are invaded, we do not know how far this invasion has extended through the lymphatic system or through or into the blood stream.

NECESSARY DIAGNOSTIC DATA: PREOPERATIVE

It is our opinion that many patients in our own clinic as well as elsewhere are subjected to radical treatment for cancer of the bladder without complete preoperative diagnostic data, which interfere with proper selection of cases. A review of the histories of our patients who submitted to cystectomy reveals that radical surgery or an attempt at removal of cancer of the bladder was delayed an average of 3½ years. This observation suggests that diagnostic methods that we are now using are incorrect or/and that treatment short of complete removal was not attempted during this long interval that was not curative and permitted the cancer to spread or metastasize and become incurable. Surgeons interested in removal of all of the cancer did not see these patients early enough to apply radical treatment while the cancer was graded one or possibly two in malignancy or while it was small or before it had metastasized or invaded additional structures.

We are in the habit of looking for gross hematuria as the cardinal and first symptom. Twenty per cent of our patients who submitted to cystectomy had no gross bleeding in their early history. It is our opinion that most tumors of the bladder produce blood and other cells in the urine sediment long before gross findings are observed by the patient or the physician. Every male and female patient should have a semi-yearly urinalysis; if microscopic blood cells are found in the urine sediment a complete urologic examination is indicated. Blood cells that appear in the urine of patients who are being examined for other conditions should not be forgotten. These may indicate the presence of a small tumor on the mucosa of the bladder. Every urologist in the course of doing a routine study for some other reason has found unsuspected tumors of the bladder that were producing no symptoms and never had produced gross hematuria. If we are ever going to discover early cancer of the bladder we must not wait until gross hematuria occurs but we must search for and discover the cause of red blood cells in the urine.

UROGRAMS

In many cases the diagnosis was made during radiography done for other conditions. These patients had urinary difficulty and frequency indicating the use of excretory urography, and the cystogram incident to it, as a diagnostic procedure. The cystogram revealed the presence of deformity or deformities that were produced by cancer growing on the mucosa of the urinary bladder.

BIOPSY: TRANSURETHRAL

We are of the opinion that the removal of bits of tissue from bladder tumors transurethrally either with the electrically activated resectoscope, the cold knife type, or rongeurs may not give satisfactory information concerning the character of the tumor. The cold knife or rongeur and the biting or cutting instruments that do not have the activated electric loop obtain better specimens. These specimen-taking instruments however may not remove sections of tissue from that portion of the bladder in which we are most interested; the attachment of the tumor to the bladder wall. Dr. Archie Dean of New York has reported that 58 per cent of the specimens examined through the microscope of the entire bladder tumor differed from the microscopic examination made on biopsy specimens removed through the cystoscope, and that 50 per cent of these, that is the operated bladder specimens, were of a greater degree of malignancy than was found in the bits of tissue removed transurethrally. Following bitter experience, most urologists have learned that all tumors of the urinary bladder are malignant, and that no tumor located here is better than its worst part. It is impossible during every cystoscopic examination to obtain a clear view of the entire tumor with its attachments to the bladder wall and the character of the adjacent bladder mucosa. When these conditions exist a specimen from the proper area of the tummor and its attachments may not be obtained transurethrally. The experienced cystoscopist can make a more accurate diagnosis of the presence of malignant change and its grade when he can view the entire bladder tumor so that all areas including its attachments to the bladder can be easily inspected, than the pathologist when he examines only a bit of tissue removed transurethrally from any portion of the tumor. It is important to remember however that the cystoscopist cannot with any instrument see through the bladder wall, so that he does not know if invasion has occurred into the perivesical tissues. This information is important as a diagnostic as well as a prognostic feature.

Dr. Melicow writes that a correct interpretation of a bladder biopsy is contingent upon the coordination of urologist, technician and pathologist. A properly prepared, adequate sample of the whole tumor is essential to a true evaluation.

ETIOLOGICAL FACTORS

To a considerable extent cancer in man is an environmental and occupational disease. Diagnostic data should include and evaluate certain etiological factors that may be operative when spontaneous tumors occur, when multiple tumors are found and when widespread local recurrences develop not in the original site. Why are tumors of the urinary bladder four times more frequent in males? and why are they located more often on or in the trigone area?

It is our opinion that there can be and frequently is a carcinogenic predisposition on the part of transitional epithelium of the urinary tract and that there can be carcinogenic stimulators in the urine so that when small tumors are removed from the bladder the cause of their being there is not necessarily removed. This is one of the reasons why we believe that diversion of the urinary stream should be used as a palliative measure more frequently and should be done earlier than is the present mode. Many of us have observed regression in extent and number of bladder tumors when diversion of the urinary stream to the skin or to the bowel has been done. This clinical observation indicates that a carcinogenic predisposition may be present in the epithelium and carcinogenic stimulators may be present in the urine. Certainly these etiological features should be considered in the careful diagnosis and treatment of these individuals.

Carcinoma of the urinary bladder invades the prostate gland frequently, and occurs in the trigone area more frequently. Carcinoma of the prostate gland invades the bladder, and tumors in these areas may have differing pathological structure. Many urologists believe that there is a relationship between these tumors and that they may be gonad controlled. Here again these etiological features must be taken into consideration as diagnostic aids and certainly are helpful when therapy is being planned. Some surgeons give patients who have tumors of the trigone, the bladder neck and posterior urethra, estrogen, just as they do for gonad related carcinoma of the prostate gland.

A recent monograph concerning cancer in general and written by a pathologist deals with biology in relation with development and control and growth of cancer. This writer is quite sure that all the transitional type epithelial structures within the urogenital tract are gonad related. This writer quotes some pathological and experimental evidence and points to these observations as not only a possibility but in his opinion a reality.

All of our patients have biopsy specimens removed for examination. We take several of these and are cognizant of the fact that we cannot with the cystoscope or with the examination of the biopsy specimen get all the information that we should have before cystectomy is contemplated.

We are much surprised to find in our group of patients that required cystectomy that the average age was 56½ years, which is 4 or 5 years younger than in other reported series. Many had previous treatment before they saw us.

Bimanual palpation of the bladder has not been so useful as has been reported by other observers. Although done under anesthesia, in many instances we were unable to feel induration from fairly large tumors in the bladder. Our technique may be at fault.

SURGICAL EXPLORATION: DIAGNOSTIC AID

Because of the many errors we encountered in the interpretation of the pathological study of biopsy specimens taken from any place in the tumor or from several places in the tumor, we have found it necessary to surgically explore the bladder and the surrounding structures, not only to obtain a satisfactory biopsy but to determine the extent of spread through the bladder wall, and the invasion of adjoining structures. We believe that this is a correct and a very useful method of diagnosis before cystectomy is contemplated. At the same time we believe that the first stage in the operation of removing the urinary bladder for cancer may be performed; i.e. the diversion of the urinary stream into the bowel or into the skin. We believe that there is no better way of obtaining information concerning spread or metastasis than the surgical exploration. I think that if this were used more often it would save many patients severe prolonged operations that cannot possibly succeed in ridding them completely of cancer.

The use of the x-ray and ureteral catheter to explore the upper urinary tract and to estimate the functional capacity of the kidney and size of the ureters are very necessary adjuncts. In addition to the use of excretory urography to locate possible lesions in the upper urinary tract and to determine the individual function of the kidneys, this diagnostic aid may be used to reveal shadows of tumors within the bladder and in some instances by taking contrast and lateral views, the size and location of the pedicle of the tumor may be determined. This is helpful in cases where there are large tumors and when it is impossible to view them through the cystoscope.

We are very careful to make all necessary x-ray and other examinations that may reveal the presence of metastases from tumors of the bladder. These occur early; they are not late manifestations as was frequently believed 20 years ago. We have seen distant metastases from tumors of the bladder that had not completely invaded the bladder wall. Unsuspected, symptomless metastases to bone may go overlooked and may not be found by x-ray at the time that surgery is contemplated. In one instance, two metastatic nodules were found in the skin. Patients who have metastases to distant areas are not subjected to cystectomy.

Another diagnostic aid that has not been used as frequently as it should and would be very, very helpful in certain instances is the examination of the urinary sediment for cancer cells. The technique of the examination of the urinary sediment for cancer cells has been improved and somewhat simplified. It should be used more frequently. It is very useful in follow-up examinations postoperatively. Is there local metastasis or recurrence?

Another diagnostic aid that may reveal information helpful in finding the type of therapy to be used in cancer of the bladder is the examination of the recto-sigmoid area when ureterosigmoidostomy is contemplated. Very recently we were about ready to implant the ureters into the sigmoid when we discovered that this patient had an incompetent rectal sphincter. Recently, on exploration we found tumors in the sigmoid that interfered with the planned treatment of bowel implantation of the ureters. A radiogram of the colon and sigmoidoscopic examination should be done.

Since postoperative complications may arise following the implantation of the ureters into the bowel, it is very necessary that the urologist knows preoperatively the character of the ureters, the comparative function of each kidney and total renal function. The operating surgeon will be able to compare and evaluate what he sees on the postoperative film with the condition before operation and thus obtain a better idea of the importance of the complications that may have developed.

The complete urological examination of male patients may reveal pathological conditions in the prostate gland: hyperplasia or other obstructive conditions which may produce changes apparent in the ureter and the kidney pelvis.

Before the surgeon plans his surgical approach and attack on cancer of the urinary bladder he must obtain all possible information concerning any and all previous treatment that may have been given to the patient. Was a tumor of the bladder fulgurated, was transurethral resection done, were radon seeds used or some surgical procedure?

A correct evaluation of the patient's cardiovascular system must be obtained. Can these organs and structures withstand the trauma and insult incident in a prolonged operation like cystectomy?

The preoperative care of the patients who submit to cystectomy will include a study of the character of the blood. Preoperative treatment may be necessary so that these patients are brought to the operating room in as good nutritional state as is possible.

When the surgeon is in possession of all these data and has decided that cystectomy and urinary diversion are to be done, the patient and his relatives must be appraised of the magnitude of the operation, the possible mortality, the possible changes that may be made in his anatomy and how this may affect his social and sexual habits. We still believe that the implantation of the ureters into the skin is not being used as frequently as it should because of the difficulty of handling the exit of the ureters and the urine on the skin. Satisfactory plastic operations on the skin and apparati will catch the urine so that the patient can care for himself. For many years a lateral anus or colostomy was refused by many patients because they were socially ostracized and physically crippled. Greater effort to make satisfactory apparati and better operative procedure now control the exit of the large bowel to the skin; the same conditions should now exist when cutaneous ureterostomy is done.

PATHOLOGY

During one of the urologic seminars conducted by the Los Angeles Urological Society, one of us (G.J.T.) discussed with Dr. J. R. McDonald, pathologist of of the Mayo Clinic, who pays particular attention to lesions of the urogenital tract, the difficulties of interpreting the pathologic diagnosis of the biopsy specimens removed through the cystoscope. Dr. McDonald recognized the inadequacy of these bits of tissue and suggested the following criteria as all-important in the pathological diagnosis of carcinoma present in the bladder and what may be expected after a tumor has been partially or completely removed. First, identification of the types of carcinoma cells present in the specimen, whether squamous, adeno, transitional or mixed; second, is the cell and tissue arrangement papillary without infiltration, papillary with infiltration, or just infiltrating?; third, has the infiltration extended? Is it confined to the wall of the bladder or has it progressed into the perivesical fat? Has vascular invasion occurred? These are very important criteria and pose several questions, some of which the cystoscopist, the urologist, or the pathologist cannot answer unless surgical exploration is done. I want to emphasize the frequent necessity of surgical exploration so that the surgeon may make a complete diagnosis of the conditions present and he can decide what he can do or what he should do.

The pathological reports of the specimens we removed at surgery or autopsy are from 24 cases that were carefully followed: 17 were transitional cell carcinomas all infiltrated; 1, squamous cell; 5, adenocarcinomas; 1 with transitional type cells also; 2 with invasion of the rectum, 2 adenocarcinomas invading the prostate gland, this beginning in the prostate gland and invading the bladder or vice versa. One of our cases in which leukoplakia was reported contained a transitional cell, not a squamous cell carcinoma. In one both transitional and squamous cells were identified; there was one case of leiomyofibrosarcoma. One specimen contained both a clear cell and a transitional cell carcinoma in the bladder. This pathological information so necessary for complete diagnosis and as an aid in determining therapy to be given could not be obtained from transurethral biopsy unless these were taken from every section of the tumor or the whole tumor was totally removed and examined. How necessary then is surgical exploration?

It is evident from these data and the diagnostic criteria suggested by Dr. McDonald that a correct pathological diagnosis of carcinoma of the urinary bladder and its extent have not always been obtained before operation. We still have much to learn about the pathological behavior of tumors of the bladder. Since metastases may occur by way of the blood vessels, it is hard to determine which patient should be operated upon and which should not. We have two instances wherein we are sure that the handling of the tumor and the bladder during cystectomy permitted or caused cancer cells to get into the general circulation so that evidence of a miliary spread occurred in 2 months following the surgical removal of the bladder. We have tried to follow what Dr. Jewett has told us about the invasion of these tumors in relation to their curability and distant metastases. If the penetration of the tumor has gone beyond the submucosa, distant spread may have already occurred.

TREATMENT

Dr. Roger Graves uses the following pathological criteria that signify cystectomy: 1) infiltrating carcinoma into the bladder wall so extensive that the visible, palpable tumor exceeds 4 cm. at the most in its greatest diameter; 2) infiltrating carcinoma, when it has penetrated the whole thickness of the bladder wall and which produces a hard area that can be felt by rectal palpation; 3) multiple papillomatosis, benign or malignant, that are so numerous and extensive that attempts to destroy all the disease would be impossible by other means; 4) carcinoma of the trigone, especially infiltrating carcinoma, bordering on or including both ureteral orifices; and 5) cancer adjacent to or involving the outlet to the bladder. On the basis of these indications Dr. Graves believes the selection of a favorable case for cystectomy is not difficult. Our selection of cases for cystectomy has not been as restricted. We have operated on some patients who were hopeless. Our experience with this operation, and that of other surgeons, will continue until we know more about the behavior of the various types of cancers that occur in the bladder, how and when they spread, etc. We hope some biological or serological test will determine when cancer is present in any organ or tissue or remains after surgical removal.

Cystectomy is not a difficult operation but is a tiresome one. One of us (G. J. T.) prefers to do it in two stages, transplanting the ureters and accomplishing surgical exploration. If cystectomy is not possible, diversion of the urinary stream is the best palliative treatment for carcinoma of the urinary bladder. Cutaneous ureterostomy is the safest but may not be the method of choice. How the bladder is to be removed will depend upon the pathological conditions that are present. We usually remove the bladder suprapubically; the dome of the bladder should be freed first. If the peritoneum or peritoneal structures are adherent, these should be dissected away and remain with the bladder. As the dissection progresses and approaches the posterior surface, then the undersurface of the bladder overriding the rectum, the dissection may be difficult and bloody. An easier line of cleavage may be obtained retropubically. The urethra distal to the prostate gland is out, the prostate gland is freed and then used as a retractor as the dissection continues upwards along the rectum until the seminal vesicles can be viewed and completely removed. The vesicles frequently contain cancer and metastases occur here frequently. Dissection of the bladder, prostate gland and vesicles in this way will develop two definite lateral pedicles, one on each side, in which most of the important blood vessels may be found. The dissection of all the tissue, fat, connective tissue, lymphatic vessels and nodes, surrounding the bladder and blood vessels should be thorough. We have not dissected nodes usually found along the large blood vessels above the pelvis but we have been careful to try to get out all of the fat and the nodes and the tissue surrounding the bladder in the bony pelvis.

In 3 instances we found carcinoma of the prostate, extending posterior to or involving the bladder. With the help of the general surgical staff, we eviscerated all of the structures in the pelvis, producing a lateral colostomy and the transplanted ureters into this stoma.

MORBIDITY AND MORTALITY

In our series we had an 18 per cent mortality, patients who died between the first and second stage or following the second stage of the operation. Two patients lived 4 years and 11 months, and 1 lived 5 years and 6 months. Eight, or 29 per cent, lived more than a year. One lived more than 2 years. The average length of time of death was 10 months after treatment.

Autopsy findings reveal that local recurrences developed frequently, which is positive evidence that we did not remove all of the cancer from the local area. When the lesion violates the bladder wall and penetrates surrounding tissues such as the blood vessels, the lymphatic nodes and vessels, in the fat and so on, it spreads and metastasizes quickly and widely. In only 9 of the 24 cases that we operated upon was there no local spread. In only 1 was there no evidence of metastases. In 14 we demonstrated widespread metastases.

We must emphasize again that metastases from cancer of the urinary bladder occurs quickly and frequently. Twenty years ago we used to think that cancer of the bladder could be treated as a local lesion for a long period of time, that it did not metastasize by any means (blood vessels, lymph vessels).

Metastases to bone occur frequently and may not be recognized. Nothing is seen on x-ray films but later on these metastases become manifest. Metastases can occur in distant areas as the skin; in 1 case, metastasis to the skin of the body was the only site of dissemination. Most of our wounds remained clean and healed well. In some, abscesses developed at the site of local metastases or in the suprapubic area in 2 cases. Pyelonephritis was present in 16. No evidence was noted in 5 of the patients. Uremia associated with other clinical causes of death was observed in 2 instances. Our ureteral implants worked pretty well, no obstruction was observed on one side or the other in 8; obstruction on both sides, 6 cases; and obstruction on one side, 5.

Cystectomy is a bilateral problem: 1) the complete removal of the cancer and the urinary bladder; 2) the maintenance of adequate renal function. These factors are intimately related one to the other and with the success of the operation. We are not pleased with the results that we have obtained in doing this formidable operation. However, we believe that some useful information has been obtained from this survey and probably some progress has been made. We know that our results can be improved.

If we are to make any suggestions from this study of our cases that have submitted to cystectomy, I think they would be as follows:

The diagnosis of the presence of cancer within the urinary bladder can be and should be made earlier.

Gross hematuria may not be the first symptom of carcinoma of the bladder. Microscopic blood cells in the urine or urinary symptoms should cause that patient to have a complete urological study.

The diagnostic methods now employed to reveal the presence of malignancy of the urinary bladder are deficient. Bimanual palpation is helpful. Surgical exploration may be necessary. All tumors of the urinary bladder are malignant. No tumor is better than its worst part.

Cystectomy is not a method of treatment for grades 3 and 4 malignancies of the bladder but should be applied when the grade of malignancy is not greater than grade 2 and when the cancer is confined to the lumen of the bladder.

Metastases in carcinoma of the bladder occurs early and may be widespread with any degree of malignancy and sometimes before the diagnosis of cancer of the bladder is made.

Diversion of the urinary stream into the sigmoid or into the skin is the best palliative treatment. Implantation into the skin is the safest method.

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HYDRODYNAMICS OF UPPER URINARY TRACT AFTER MUCOSAL URETEROSIGMOIDOSTOMY: CASE REPORT*

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The following case is reported because it is unique, and because it offers information relative to hydrodynamics of the urinary tract, acidosis and uremia following ureterosigmoidostomy by the mucosa-to-mucosa method. It demonstrates that relatively normal existence is possible despite the passage of a fecal stream through the kidneys if obstruction is absent at the ureterosigmoid juncture. Free communication between the renal pelves and the bowel is demonstrated by spontaneous air pyelograms, reflux pyelograms after enemas, and by the prompt healing of the nephrostomies after removal of the nephrostomy tubes. High intracolonic pressures presumably are transmitted to the renal pelves. It is suggested that acidosis and uremia may follow as a result of systemic urinary backflow.

CASE REPORT

A white woman, 47 years old, entered the San Diego County General Hospital complaining of total hematuria, and severe urgency of 3 months' duration. The associated symptoms were general malaise, weakness, and weight loss of 11 pounds. A smooth, solid, ovoid, freely movable tumor, 15.0 cm. in diameter, was palpated in the pelvis anterior to and separate from the uterus.

The systolic blood pressure was 210 mm. of mercury and diastolic was 120. The urine contained innumerable red and occasional white blood cells. Urine culture resulted in a growth of E. coli and P. vulgaris. The hemoglobin was 68 per cent, red blood cells 3,920,000, and white blood cells 11,700 with a slight shift to the left. The blood urea nitrogen was 23.9 mg. per cent.

Serial roentgenograms of the skeletal system and a roentgenogram of the chest were normal.

Cystoscopic examination revealed a large, fungating carcinoma which filled the bladder. The ureteral orifices were not seen. Indigo carmine did not appear in 30 minutes. Right hydronephrosis, grade 3, was seen on excretory urograms. No dye appeared on the left side (fig. 1, *A*).

The pathologic diagnosis was papillary carcinoma, grade 2.

In view of these observations and the desperate condition of the patient, bilateral nephrostomy was recommended and was accomplished without incident. A double left upper ureter and pelvis necessitated two nephrostomy tubes.

The condition of the patient improved rapidly. The previously nonfunctioning left kidney excreted up to 800 cc daily, and the blood urea nitrogen dropped to 14.6 mg. per cent. Pyelo-ureterography through the nephrostomies disclosed

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Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 10, 1950.
* Joseph F. McCarthy prize essay.

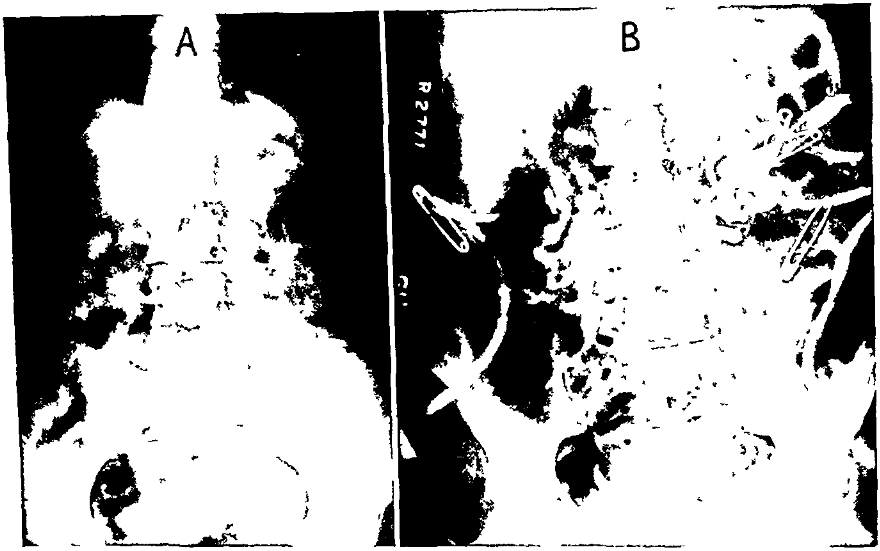

FIG. 1. *A*, admission excretory urogram at 60 minutes, demonstrating grade 3 right hydronephrosis and no function on left *B*, pyelo-ureterograms through nephrostomy tubes showing decrease in right hydronephrosis. Double pelvis on left is shown. Both ureters are tortuous and dilated.

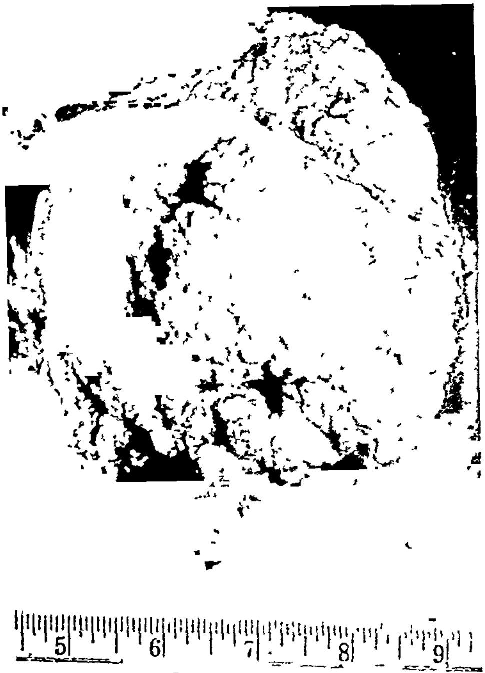

FIG. 2. Bladder and its tumor

that the right hydronephrosis was much decreased, and that a grade 2 hydronephrosis was present on the left side. The ureters were elongated, tortuous, dilated and obstructed in their intramural portions, the right partially and the left completely (fig. 1, *B*).

Total cystectomy with ligation of the ureters was performed 14 days after nephrostomy (fig. 2). No evidence of metastasis was found. The patient's condition at this time did not warrant ureterosigmoidostomy. Convalescence was uneventful.

One month after cystectomy, bilateral ureterosigmoidostomy was done using the mucosa-to-mucosa technique. The patient's postoperative course was remarkably smooth. Her temperature rose to 103F on the first day after transplantation, but was normal thereafter. Immediately after the anastomosis, the blood urea nitrogen rose to 23 mg. per hundred cubic centimeters but was 11.6 mg. by the eleventh postoperative day. On the third postoperative day, gross feces and gas were observed coming from the nephrostomy tubes. The patient evinced no untoward reaction to the fecal current through her upper urinary tract. The nephrostomy tubes were clamped. Feces and gas literally exploded from the nephrostomy tubes when they were released for irrigation. Pyelo-ureterography through the nephrostomies demonstrated free communication with the sigmoid bilaterally (fig. 3). Beginning the fifth day after the transplantation, the nephrostomy tubes were removed in series. All drainage from the rectum promptly ceased and the contents of the bowel drained profusely from all renal fistulas. These gradually closed, however, and were completely healed by the sixteenth day following the anastomosis.

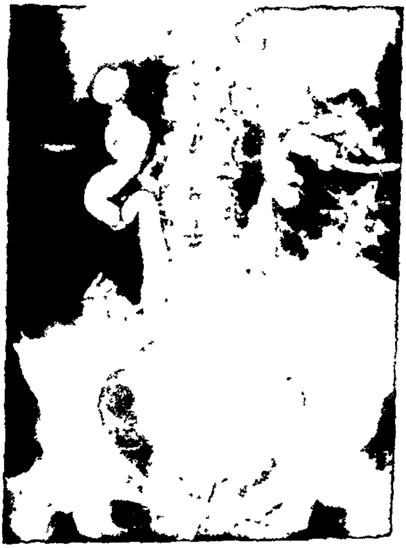

FIG. 3. Pyelo-ureterograms through nephrostomy tubes after ureterosigmoidostomy demonstrating free communication with sigmoid

Since discharge from the hospital the patient has remained afebrile and asymptomatic and has returned to her occupation as barmaid. The blood pressure has decreased to 138 over 90. The cloaca has functioned well. However, blood chemistry determinations have belied the clinical course: the urea nitrogen has gradually increased, the carbon dioxide combining power has decreased, although the patient has gained weight, strength and well being (fig. 4, *A*).

Excretory urograms since the anastomoses have not been sufficiently distinct for reproduction. Dye has been seen in some minor calyces, but the medium never has displaced the gas sufficiently to outline the pelves and the ureters completely.

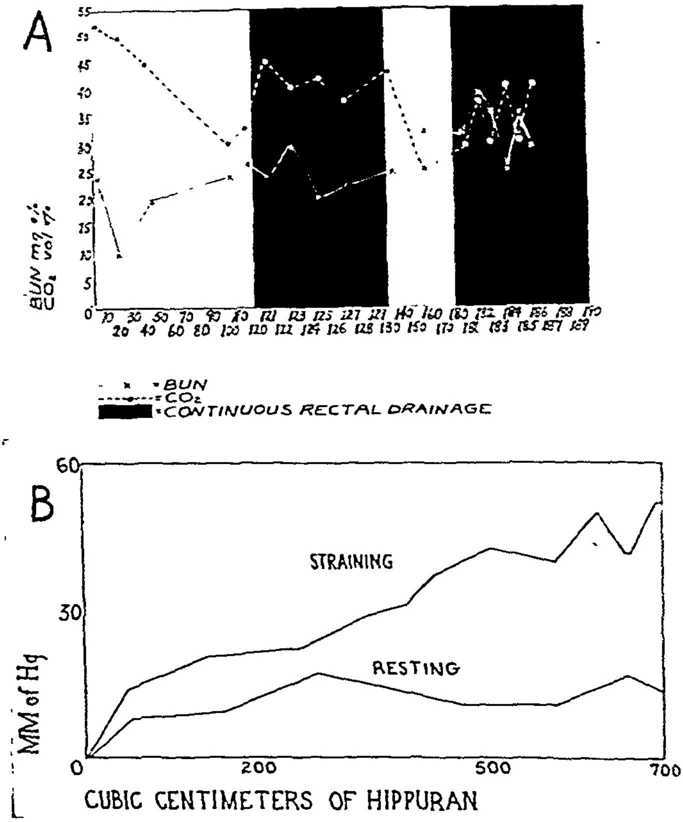

FIG. 4. *A*, values of blood urea nitrogen and carbon dioxide combining power following ureterosigmoidostomy by mucosa-to-mucosa method. Gradual development of uremia and acidosis. Tendency towards correction on continuous rectal drainage. *B*, intracolonic pressure readings obtained during resting and straining. Resting values correspond with normal. High straining values not achieved. Values are, however, high enough to produce systemic urinary backflow.

Sigmoidoscopy 116 days after the anastomoses disclosed normal bowel mucosa. The ureteral orifices were not visualized.

Certain interesting experimental data were obtained, but determination of the intrapelvic pressure was overlooked. The pressure of expulsion of gas and feces through the nephrostomy tubes was estimated at 40 to 50 mm. of mercury.

According to Best and Taylor, normal resting intracolonic pressure is 20 mm. of mercury, and the defecation reflex occurs at 40 to 50 mm. of mercury. Straining produces pressures of 100 to 200 mm. of mercury. Figure 4, *B* illustrates intracolonic pressure in this patient at rest and with straining, after instillation of increasing quantities of a 20 per cent hippuran solution. Pneumopyelograms at resting pressures, obtained at will, are shown in figure 5, *A*. Pyelo-ureterograms obtained at resting pressures with the hippuran enema are shown in figure 5, *B*.

The values of the blood urea nitrogen and of the carbon dioxide combining power after ureterosigmoidostomy are presented in figure 4, *A*. The uremia and acidosis finally recurred and persisted. Continuous rectal drainage by catheter for seven day periods tended to restore normal values.

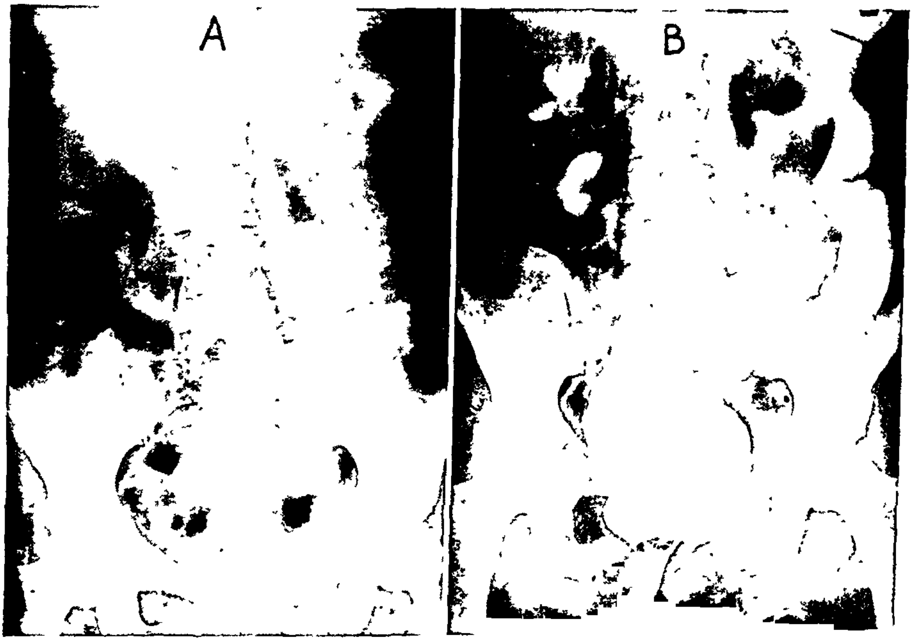

FIG. 5. *A*, plain film of abdomen shows bilateral pneumopyelograms. *B*, hippuran enema at resting pressure showing reflux up right ureter and left pneumopyelogram. Colon filled to splenic flexure.

DISCUSSION

Imbalances of blood chemistry values following ureterosigmoidostomy have been noted only recently. Ferris and Odel report that 80 per cent of their series of patients had hyperchloremic acidosis. The majority of these also had elevated blood urea values.

These men have postulated that selective rectal absorption of chlorides occurs producing a relative sodium deficiency and acidosis. However, the exact mechanism of this process and the elevated levels of blood urea are not explained. Sauer and his coworkers discounted reabsorption from the bowel as a factor because they noted a rise in the blood urea nitrogen immediately postoperatively when the patients were on continuous rectal tube drainage, and a fall later on when the rectal tube was removed.

The mechanism producing acidosis and uremia possibly may be pyelorenal backflow. Reflux pyelograms and the observed fecal drainage from the nephrostomies demonstrate the free communication of fluid and hence of intrapelvic and intracolonic pressures in the case reported here. Others have also noted reflux following mucosa-to-mucosa anastomosis.

Pyelorenal backflow and upper urinary tract pressure studies have been reported by various authors. The pressure required to produce pyelorenal backflow in normal kidneys varies from 20 to 160 mm. of mercury. In hydronephrotic kidneys, pressures of only 10 to 15 mm. of mercury will cause pyelorenal backflow. Data obtained in our patient reveal that pressures of sufficient magnitude to produce this phenomenon are directly transmitted to the renal pelves from the colon. In our patient, as in those of others, there was a tendency toward correction of the chemical imbalance on continuous rectal drainage.

Comparison has not been made of blood chemistry imbalances following the Coffey tunnel type of operation and those following the mucosa-to-mucosa technique. Theoretically, reflux after the Coffey type operation does not occur and pyelorenal backflow would not be a factor. However, the absence of reflux never has been proved clinically.

SUMMARY

A case is presented in which free communication and transmission of pressure between the colon and the renal pelvis occurred following mucosa-to-mucosa ureterosigmoidostomy. This was shown by explosive passage of feces and gas through nephrostomies, and by air and opaque reflux pyelograms. The free communication is demonstrated to be acceptable in some respects by the prompt healing of the nephrostomies, the well being of the patient and the absence of febrile episodes. Nevertheless a fecal stream through the kidneys could not conceivably produce any benefit. Speculation is offered concerning the role of intrapelvic pressures, transmitted from the colon, causing systemic backflow of urine in the production of acidosis and uremia. We believe that subsequent observation will demonstrate the deleterious effect of free transmission of intracolonic pressures to the renal pelves.

REFERENCES

Baretz L. H.: J. A. M. A., **106:** 980, 1936.
Best, C. H. and Taylor, N. B.: Physiological Basis of Medical Practice. Baltimore: Williams and Wilkins, 1945, 4th ed., pp. 377–398.
Bird, C. E. and Moise, T. S.: J. A. M. A., **86:** 661, 1926.
Bradley, S. E. and Bradley, G. P.: J. Clin. Investigation, **26:** 1010, 1947.
Bush, Coffman, Montgomery and Swann: Texas Rep. Biol. & Med., **7:** 492, 1949.
Coffey, R. C.: West. J. Surg., **41:** 311, 1933.
Coffey, R. C.: Surg., Gynec. & Obst., **47:** 593, 1928.
Cordonnier, J. J.: J. Urol., **63:** 276, 1950.
Drury, D. R., Henry, J. P. and Goodman, J.: J. Clin. Investigation, **26:** 945, 1947.
Ferris, D. O. and Odel, H. M.: J. A. M. A., **142:** 634, 1950.
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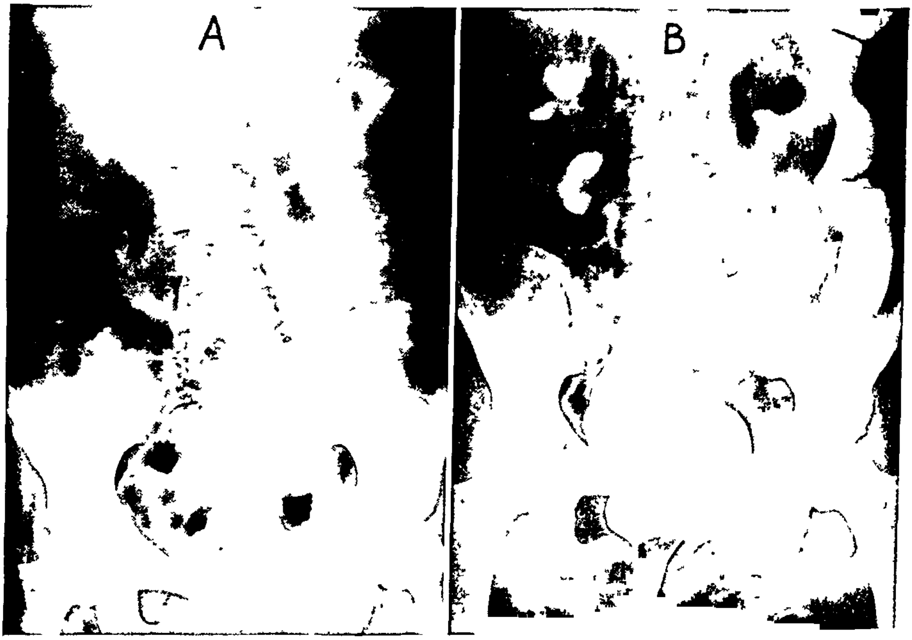

FIG 5 *A*, plain film of abdomen shows bilateral pneumopyelograms *B*, hippuran enema at resting pressure showing reflux up right ureter and left pneumopyelogram Colon filled to splenic flexure.

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REFERENCES

Baretz L. H.: J. A. M. A., 106: 980, 1936.

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Bird, C. E. and Moise, T. S.: J. A. M. A., 86: 661, 1926.

Bradley, S. E. and Bradley, G. P.: J. Clin. Investigation, 26: 1010, 1947.

Bush, Coffman, Montgomery and Swann: Texas Rep. Biol. & Med., 7: 492, 1949.

Coffey, R. C.: West. J. Surg., 41: 311, 1933.

Coffey, R. C.: Surg., Gynec. & Obst., 47: 593, 1928.

Cordonnier, J. J.: J. Urol., 63: 276, 1950.

Drury, D. R., Henry, J. P. and Goodman, J.: J. Clin. Investigation, 26: 945, 1947.

Ferris, D. O. and Odel, H. M.: J. A. M. A., 142: 634, 1950.

Forster, R. P.: Am. J. Physiol., 150: 523, 1947.

Fuchs, F.: J. Urol., 23: 181, 1930.

Hinman, F.: Principles and Practice of Urology. Philadelphia and London: W. B. Saunders Co., 1936, pp. 232–239 and pp. 487–513.
Hinman, F.: Surg., Gynec. & Obst., **44:** 592, 1927.
Hinman, F. and Lee-Brown: J. A. M. A., **82:** 607, 1924.
Hinman, F. Jr.: Personal communication.
Hinman, F. Jr.: In discussion on Cordonnier.
Jewett, H. J.: In discussion on Ferris and Odel.
Levy, S. E., Morton, F. M., Tinsley, R. H., and Blalock, A.: Surgery, **1:** 238, 1937.
Marshall, V. F.: J. Urol., **58:** 244, 1947.
Marshall, V. F.: *In discussion on Ferris and Odel.*
Marshall, V. F. and Gardner, J. S.: Surg., Gynec. & Obst., **81:** 559, 1945.
Narath, P. A.: J. Urol., **43:** 145, 1940.
Nesbit, R. M.: Ann. Surg., **130:** 796, 1949.
Nesbit, R. M.: In discussion on Cordonnier.
Poth, E. J.: Surg., Gynec. & Obst., **74:** 221, 1942.
Redish, I., West, J. R., Whitehead, B. W. and Chasis, H.: J. Clin. Investigation, **26:** 1043, 1947.
Rolnick, H. C. and Singer, P. L.: J. Urol., **57:** 834, 1947.
Sauer, H. R., Blick, M. S. and Buchwald, K. W.: Surg., Gynec. & Obst., **89:** 299, 1949.
Scott, D. E.: J. Urol., **30:** 39, 1933.
Trattner, H. R., Wright, H. B. and Barlow, O. W.: J. Urol., **23:** 441, 1930.
Vermooten, V.: J. Urol., **32:** 266, 273, 1934.
Vermooten, V., Spies, J. W. and Neuswanger, C. H.: J. Urol., **32:** 261, 1934.
Weyrauch, H. M.: Personal communication.
Winton F. R.: Physiol. Revs., **17:** 408, 1937.

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COMPLICATIONS AND END RESULTS FOLLOWING URETERO-INTESTINAL ANASTOMOSIS

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Uretero-intestinal anastomosis as a method of diverting the urinary stream above the bladder is not difficult technically, but when carcinoma is the indication for the procedure, with or without cystectomy, the operation assumes major proportions. Patients with cancer generally are poor surgical risks.

In the interests of increasing our knowledge of the complications and end results of uretero-intestinal anastomosis, particularly the physiochemical disturbances that occur as a result of the procedure, an analysis has been made of 33 cases taken from the urological service of the University of Southern California at the Los Angeles General Hospital and from our private practice.

SEX AND AGE

Distribution as to sex and age is given in tables 1 and 2.

INDICATIONS AND TYPES OF ANASTOMOSES

The indications for the operation and the types of anastomoses employed are presented in table 3.

ASSOCIATED PATHOLOGIC LESIONS

In table 4 are analyzed the local and general associated pathologic lesions encountered. In 3 of the patients the primary disease was the only lesion present. Infection and/or obstruction of the urinary tract accompanied the primary lesion which constituted the indication for uretero-intestinal anastomosis in many instances. In some patients multiple associated local or systemic conditions increased the hazard of operation. Almost all patients were poor surgical risks because of impaired general health as a result of intense symptoms referable to the bladder, lack of adequate diet and of rest and because of their age. The majority had frequency, nocturia, urgency and dysuria and many had suffered intractable pain. Seventy-six per cent also had gross hematuria. In 60 per cent symptoms had been present for six months or less before operation.

DEGREE OF MALIGNANCY

In every instance of carcinoma of the bladder or of the urethra, biopsy was done prior to the uretero-intestinal anastomosis. Table 5 indicates the grade of malignancy in these 27 cases. Several patients with lesions of grade 2 or grade 3 malignancy had had resections prior to the operations reported here. During the intervening periods, which ranged from 3 months to 1 year, the grade of malignancy had increased.

Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 10, 1950.

TYPE OF SURGERY

The operation was done as a one stage procedure in 31 patients of the series, including 11 in whom both uretero-intestinal anastomosis and total cystectomy was carried out. Two patients had a two stage operation of which the second stage consisted in cystectomy (table 6). In 9 patients only one ureter was transplanted (table 3). The opposite kidney had been removed in 6 instances and in 3 it was thought functionless. In 2 of the latter, however, renal function returned and the passage of urine through the bladder caused a recurrence of the primary complaint.

TABLE 1. *Distribution as to sex*

	NUMBER PATIENTS
Male	20
Female	13
Total	33

TABLE 2. *Distribution as to age*

YEARS	NUMBER PATIENTS
10-25	1
25-50	6
50-60	9
60-70	11
70-80	6
Total	33

TABLE 3. *Indications for and types of anastomoses*

	COFFEY NO 1	COFFEY NO 2	MUCOSA TO MUCOSA	TOTAL
Carcinoma				
bladder	5 (1)	3 (3)	18 (3)	26 (7)
urethra	—	1	—	1
cervix	—	—	1	1
uterus	—	1	—	1
rectum	—	—	1	1
Cystitis				
tuberculous	1 (1)	—	—	1 (1)
interstitial	—	1	—	1
Exstrophy of bladder	—	—	1 (1)	1 (1)
Total	6	6	21	33

Note Numbers in parentheses represent cases in which only one ureter was anastomosed to the intestine.

POSTOPERATIVE COMPLICATIONS

Table 7 records the complications encountered during the first postoperative week. Adynamic ileus occurred most often and at times was the most troublesome complication. The mucosa to mucosa technique gave the best immediate postoperative result so far as infrequency of complications was concerned.

TABLE 4. *Associated pathologic lesions*

ASSOCIATED LESION	INDICATIONS FOR URETERO-INTESTINAL ANASTOMOSIS					
	Cancer			Cystitis		Exstrophy of Bladder
	Bladder	Urethra	Cervix	Interstitial	Tuberculous	
Hydronephrosis	10	—	1	1	1	—
Chronic pyelonephritis	9	—	—	—	—	1
Functionless kidney	5	—	—	—	—	—
Pyonephrosis	3	—	1	1	1	1
Prostatic obstruction	2	—	—	—	—	—
Cancer of prostate	1	—	—	—	—	—
Vesical calculi	1	—	—	—	—	—
Secondary anemia	3	—	—	—	—	—
Hypertensive heart disease	2	1	—	—	—	—
Arteriosclerotic heart disease	3	—	—	—	—	—
Syphilis	1	—	1	—	—	—
Duodenal ulcer	1	—	—	—	—	—

TABLE 5. *Grade of malignancy in vesical and urethral tumors*

LESION	I	II	III	IV	TOTAL
Cancer					
bladder	2	9	13	2	26
urethra	—	1	—	—	1
Total	2	10	13	2	27

TABLE 6. *Type of surgery*

INDICATION	ONE STAGE		TWO STAGE
	Without Cystectomy	With Cystectomy	With Cystectomy
Cancer			
bladder	14	11	1
urethra	—	—	1
All other lesions	6	—	—
Total	20	11	2

PHYSIOCHEMICAL DISTURBANCES

It is becoming increasingly apparent that, during the initial postoperative period, close watch for electrolyte imbalance is of utmost importance. A diet of insufficient caloric value, reabsorption of urinary products from the rectum and obstruction and/or infection of the upper urinary tract all contribute to rapid alteration of the electrolyte balance in these patients.

TABLE 7. *Clinical complications during first postoperative week*

	COFFEY NO 1 NUMBER PATIENTS	COFFEY NO. 2 NUMBER PATIENTS	MUCOSA TO MUCOSA NUMBER PATIENTS	TOTAL INSTANCES
Ileus.	3 (50%)	3 (50%)	6 (29%)	12
Pyelonephritis	—	3 (50%)	3 (14%)	6
Leakage of urine	3 (50%)	1 (17%)	2 (10%)	6
Wound infection	2 (33%)	2 (33%)	2 (10%)	6
Peritonitis	—	1 (17%)	3 (14%)	4
Jaundice	—	1 (17%)	1 (5%)	2
Atelectasis	1 (17%)	—	—	1
Pneumonia	—	—	1 (5%)	1
Wound dehiscence	—	1 (17%)	1 (5%)	2

Note: The percentages in parentheses relate to total operations by the various techniques: the Coffey No. 1 technique was employed in 6 patients, the Coffey No. 2 in 6, and the mucosa to mucosa in the 21 other patients in this series.

TABLE 8. *Changes in blood chemistry during the first postoperative week*

	NPN OVER 45 MG	CO_2 BELOW 40 VOLUMES	POTASSIUM BELOW 15 MG
Coffey No. 1	2 (33%)	—	—
Coffey No. 2	3 (50%)	—	—
Mucosa to mucosa	9 (43%)	8 (38%)	13 (62%)

Note: The percentages in parentheses relate to the total operations by the various techniques.

TABLE 9. *Changes in blood chemistry from the second week to one month after operation*

	NONPROTEIN NITROGEN			CO_2 BELOW 40 VOLUMES	POTASSIUM BELOW 15 MG
	Remained Normal	Elevated (Uremia)	Returned to Normal after Primary Rise		
Coffey No. 1	2 (33%)	2 (33%)	2 (33%)	—	—
Coffey No. 2	2 (33%)	3 (50%)	1 (17%)	—	—
Mucosa to mucosa	9 (43%)	7 (33%)	5 (24%)	9 (43%)	6 (29%)

Note: The percentages in parentheses relate to the total operations by the various techniques.

Table 8 illustrates the variations in blood nonprotein nitrogen, carbon dioxide and potassium during the first postoperative week. In the early operations done by the Coffey No. 1 and No 2 technique we were not aware of these rapidly changing electrolyte values so that complete data on blood chemistry were not obtained during the immediate postoperative course.

Table 9 illustrates electrolyte embalances observed during the late postoperative period in this series. These data indicate that an increase in nonprotein nitrogen appeared early in some patients and that their blood chemistry values returned to normal during the second postoperative week. However, in a few the values remained elevated while in others they became elevated during this period of their convalescence. Evidence of reabsorption of urinary products from the rectal mucosa was obtained through observation of blood chemistry values in 1 patient: This woman was able to hold her urine in the rectum for periods as long as eight hours at which times her nonprotein nitrogen would rise to 75 to 80 mg. per hundred cubic centimeters. She was instructed to empty her rectum every 3 or 4 hours, during which regimen the nonprotein nitrogen would drop to 35 to 40 mg.

TABLE 10. *Results as to survival*

	NUMBER PATIENTS
Died within two weeks:	
Coffey No. 1	1
Coffey No. 2	3
Mucosa to mucosa	3
Died with 2 months to 1 year	16
Alive at present (3 months to 3 years after operation)	10
Total	33

TABLE 11. *Principal causes of death*

	COFFEY NO 1	COFFEY NO 2	MUCOSA TO MUCOSA
Carcinoma	1	2	6
Uremia and pyelonephritis	4	4	3
Intestinal obstruction	—	—	3
Peritonitis	1	—	2
Myocardial fibrosis with failure	—	—	1
Pneumonia	—	—	1
Pulmonary embolus	—	—	1

Note: In many patients there was more than one possible cause for death.

In combating hypopotassemia we have used exclusively the intravenous administration of potassium chloride. Since these patients frequently have adynamic ileus they are unable to derive benefit from oral administration of the drug, and because of the uretero-intestinal anastomosis rectal administration of potassium likewise is ineffective.

POSTOPERATIVE HOSPITALIZATION

The average period of hospitalization following operation in the 26 patients who lived more than 2 weeks after the surgical procedure was 37 days. In 22 of these patients this period averaged 25 days, the stay in the hospital being prolonged in the other 4 patients because of jaundice in 1 (105 days), a leukotomy in 1 (52 days) and for additional urologic surgery in 2 others.

MORTALITY

The mortality in the series is presented in table 10. The immediate mortality was 21 per cent (7 patients). In the patients subjected to the Coffey No. 1 technique it was 17 per cent (1 of 6 patients), in those in whom the Coffey No. 2 technique was employed 50 per cent (3 of 6 patients), and following the mucosa technique 14 per cent (3 of 21 patients). Of the 16 patients who died within 2 months to 1 year after operation, 9 in whom the operation had been done as a palliative measure died of the malignant disease for which surgical intervention had been undertaken, 3 died of uremia, 3 of intestinal obstruction and 1 of myocardial fibrosis.

CAUSES OF DEATH

Table 11 lists the principal causes of death in the series. In many patients there was more than one cause for death, for example carcinoma was associated frequently with chronic pyelonephritis and uremia. Three patients had intestinal obstruction, 1 requiring resection of the gangrenous bowel (this patient died of pneumonia). Peritonitis was notably infrequent in the series, however 3 patients died early from this operative complication. It is interesting to note that 3 of the 10 patients now living were those whose primary lesion was benign, i.e., tuberculous cystitis, interstitial cystitis and exstrophy of the bladder, and that all 3 were in the early age group. The patient in whom the ureter was anastomosed to a colostomy, which had been done because of rectal carcinoma, also is alive. With the exception of the 3 patients with benign lesions, all in the series had some form of carcinoma and were poor surgical risks because of the general state of health and advanced age.

SUMMARY

Uretero-intestinal anastomosis with or without cystectomy is not a new surgical approach to the treatment of vesical cancer. It cannot be considered a solution to this grave problem, especially in the late stages of the disease when the patient's general condition is poor and the neoplasm is highly malignant. Even in well selected cases and in spite of the contribution of the antibiotics in mitigating the hazard of removal of the cancerous bladder and uretero-intestinal anastomosis, complications are numerous and the end results seldom are entirely satisfactory. It may be said, however, that the end results are more satisfactory than are those achieved by adequate radiation.

One factor contributing to the high rate of unsatisfactory end results is to be found in the ill advised conservative attitude that has dominated choice of therapy for vesical neoplasms so that uretero-intestinal anastomosis alone or in conjunction with cystectomy seldom is used until late in the course of the disease, when the patient's poor general health precludes a favorable outcome. Also, it is becoming increasingly evident that many untoward results following this operation are due to the rather severe physiochemical changes which occur postoperatively. We believe that close attention should be paid to these sequellae, particularly to changes in the levels of nonprotein nitrogen and potassium in the blood.

CONCLUSION

In reevaluating the more conservative methods of dealing with a malignant lesion of the bladder, the frequency of recurrences would indicate that a more radical method should be employed before the neoplasm becomes surgically unmanageable and the patient's condition deteriorates to a degree that forbids extensive surgery or that precludes a successful result.

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ACUTE RETENTION IN PREGNANCY

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Failure of the urinary bladder to function normally during pregnancy is uncommon. The inability of the normal bladder to adequately empty during the pregnant state is reported in but one condition; that is a retroverted uterus. Severe uterine retroflexion can result in complete obstruction to the urinary channel. The mechanism depends on an expanding retroflexed uterus securely wedged between the pubis and sacrum in which the cervix acts as the pressure point to effect urethral occlusion.

We were able to find in the available literature the report of 2 previous patients who suffered complete urinary retention in pregnancy due to uterine retroversion. Smellie (1877) reported a patient with total urinary retention in the fourth month of pregnancy. Crabtree (1912) reported the condition at the Boston Lying-In Hospital. The case we are presenting occurred in a patient, who like the others reported, was in the fourth month of gestation. In all 3 cases, the degree of retroflexion was complete so as to prevent the rise of the uterus out of the true pelvis.

CASE REPORT

A white primipara of 36 years was seen in the Emergency Room of the Louisville General Hospital because of severe constant suprapubic discomfort, and the inability to void during the previous 18 hours. Defecation had been painful and difficult for the past 2 days. Examination of the abdomen revealed a markedly distended urinary bladder and catheterization yielded 1500 cc microscopically normal urine. This patient experienced immediate relief and refused hospitalization. She was seen again the following day, having been unable to micturate since catheterization. She consented at this time to hospitalization and a complete urological study.

The general appearance of the patient was that of a young white woman not seriously nor chronically ill, but in acute discomfort. She claimed that she had been in excellent health all her life and had no previous disease of the genitourinary tract. The patient was of the belief that she was approximately 4 months' pregnant.

Physical examination revealed marked suprapubic tenderness. The urinary bladder could be palpated one finger breadth below the umbilicus. Rectal examination showed large, protruding, edematous hemorrhoids. Digital examination revealed a mass which was external to the bowel that was exerting obstructive pressure on the rectal lumen. On sterile vaginal examination a markedly retroverted uterus was palpated, the size of which coincided with a 4 months' pregnancy. There were no other abnormal findings.

The blood pressure was 114/72. There was no elevation of body temperature. The hemogram was within normal limits.

Catheterization was again easily performed and 1800 cc clear urine was obtained. The urine contained an occasional pus cell and was negative for sugar and albumin. The reaction was acid and the specific gravity was 1.024.

The following day a cystoscopic examination was performed under sodium pentothal anesthesia. The No. 18 convex Brown-Buerger cystoscope was introduced into the bladder with considerable difficulty. The urethra was displaced anteriorly and considerable depression of the instrument was necessary before it could be introduced into the bladder. Inspection of the bladder revealed an unusual degree of pressure against the posterior wall of the bladder, edema of the internal orifice and generalized vascular engorgement. The ureteral orifices were displaced laterally.

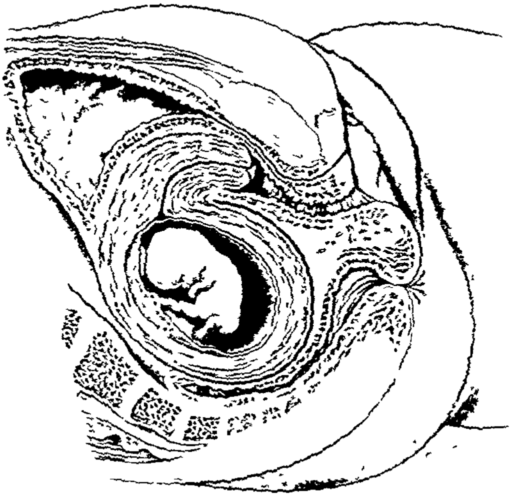

FIGURE 1

After cystoscopy a sterile bimanual pelvic examination was performed. The retroflexed uterus was replaced in the normal anatomical position and so maintained by a properly fitting pessary. Observation for the next three days disclosed complete absence of all urinary tract symptoms. The patient voided with ease. On the third day following cystoscopy only 10 cc residual urine was demonstrated. She was discharged from the hospital and followed at monthly intervals in the urology clinic. The pessary was removed 1 month after its insertion. At her last visit she was symptom free, the uterus was in its normal position and there was no residual urine.

SUMMARY

A case of complete urinary retention due to uterine pressure has been presented as the third recorded instance in the available literature. The clinical

findings of obstruction to the urinary tract and the lower bowel from a severely retroflexed uterus have been described.

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REFERENCES

CRABTREE, E G Urological Diseases of Pregnancy Baltimore Williams & Wilkins, 1942.
CURTIS, A H The management of the female urinary bladder during pregnancy. J A M A, **80:** 1126, 1923
LOWSLEY, O S, AND KIRWIN, T J Clinical Urology Baltimore Williams & Wilkins, 1944
MARTIN, E Die Harnblase wahrend der Geburt Arch f Gynak, **88:** 391, 1909
SMELLIE, W *Treatise on the Theory and Practice to Midwifery Edited by* A H McClintock London The New Sydenham Society, London, 1877

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A SUBSTITUTE BLADDER AND URETHRA, USING CECUM AS BLADDER AND ILEUM AS URETHRA

JAMES W. MERRICKS AND (BY INVITATION) R. K. GILCHRIST,
HOWARD HAMLIN AND I. T. RIEGER

From the Urological and Surgical Services of the Presbyterian Hospital of Chicago. Chicago, Ill.

In the treatment of certain tumors of the rectum, uterus, bladder and prostate, in certain congenital anomalies and in other conditions such as extensive vesicovaginal and rectovaginal fistulas, it may be highly desirable to divert the urinary stream above the bladder. Numerous operations have been designed to make life livable as well as possible after this procedure. Rubin's recent survey makes a complete review of the literature unnecessary. In general, these procedures fall into the following categories:

1) Cutaneous fistulas, which, of course, include nephrostomy, pyelostomy, ureterostomy and colostomy with ureteral transplants.

2) Implantation of the ureters into some portion of the gastro-intestinal tract left in continuity, ureterosigmoidostomy being most acceptable.

3) Implantation of the ureters into some isolated part of the gastro-intestinal tract with various types of cutaneous fistulas.

Each of those procedures has value and each has some limitation such as: a "wet" colostomy, stricturing of the transplanted ureters, recurrent pyelonephritis, incontinence and limitation of radical surgery when dealing with malignancy.

Stimulated by a study of Cortes' work on the formation of a substitute bladder from the isolated cecum with the appendix serving as the external fistula, in which incontinence was the chief disadvantage, we reasoned that a continent substitute bladder could be made from the cecum if the cut-off action of the ileocecal valve and the peristaltic action of the ileum could be utilized.

Mann and Bollman showed that an isolated piece of small intestine anastomosed in an antiperistaltic manner between the skin and the gastro-intestinal tract in the dog allowed no fecal spillage, if the antiperistaltic segment measured more than 4 to 5 inches long. The principle has been used in the Roux Y anastomosis to correct biliary stricture (Cole, et al.). Pearse found that the antiperistaltic arm should be 12 inches long to prevent regurgitation of intestinal contents. This action serves as part of our cut-off valve. The ileocecal valve is competent and prevents reflux of bowel content from the cecum into the ileum in an appreciable percentage of cases of large bowel obstruction. This action serves as the second factor to help make our cut-off valve. Appleby, as well as others, has shown recently that both ureters can be transplanted with safety to the cecum if adequate drainage is provided.

We wish to present a procedure for urinary diversion by the formation of a substitute bladder which has the following advantages:

1) There is no contamination by the fecal stream.

2) The ureteral anastomoses are easily made at any level up to the kidney, and can be covered by peritoneum.

Read at annual meeting, American Urological Association, Washington, D.C., May 31, 1950.

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REFERENCES

CRABTREE, E. G.: Urological Diseases of Pregnancy. Baltimore: Williams & Wilkins., 1942.

CURTIS, A. H.: The management of the female urinary bladder during pregnancy. J. A. M. A., 80: 1126, 1923.

LOWSLEY, O. S., AND KIRWIN, T. J.: Clinical Urology. Baltimore: Williams & Wilkins, 1944.

MARTIN, E.: Die Harnblase wahrend der Geburt. Arch. f. Gynak., 88: 391, 1909.

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1) There is no contamination by the fecal stream.

2) The ureteral anastomoses are easily made at any level up to the kidney, and can be covered by peritoneum.

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3) A cystoscope can easily be passed to the new bladder and the ureteral orifices dilated or otherwise treated if need be.

4) A device is not necessary to prevent leakage.

5) There is no limitation of radical surgery.

The new bladder is made from the isolated terminal ileum, cecum and ascending colon. Bowel continuity is reestablished by ileocolostomy and the ureters are transplanted to the new bladder. The terminal ileum is brought out to the abdomen to serve as the urethra and an indwelling catheter is left in the new bladder. Finally, the patient is taught how to catheterize himself often enough to prevent overflow leakage.

The steps in the procedure are as follows:

1) The bowel is prepared in the usual manner, with more catharsis to clean the cecum. The terminal ileum, cecum and ascending colon are thoroughly mobilized. The ascending colon is divided near the hepatic flexure and the ends are closed, so as to leave a new bladder which is 6 to 8 inches in length. Then the terminal ileum is divided 6 to 8 inches proximal to the ileocecal valve and the proximal end is closed. The mesentery is divided as far as possible towards the root.

2) Bowel continuity is re-established by ileocolostomy. At this point the operation can be terminated at any time if the condition of the patient so warrants it. The new bladder is swung downwards and to the left so that it lies transversely at the pelvic brim. The ileocecal valve should lie anteriorly to facilitate future cystoscopy. The ureters are then transplanted to the posterior wall of the new bladder.

3) The method for ureteral transplantation has most often been a modified Coffey 1.

4) Extraperitonealization of the ureters can easily be accomplished.

5) The segment of ileum is brought out to the abdomen through a stab wound. A colostomy is then made if there is need for one. Any existing pathological changes can now be eradicated or deferred until later. A Foley catheter is left indwelling for over a week and the patient is then taught to catheterize himself often enough to prevent overflow leakage.

Before attempting this operation on a human patient, it was performed on a series of dogs to acquaint ourselves with any of the difficulties which might arise, and to determine if a continent bladder could be made in this fashion.

Ten dogs were operated on with a mortality of 4 due to peritonitis and on evisceration. It is difficult to clean out the cecum in the dog. Of the remaining 6, four had satisfactory continent bladders with capacities ranging from 6 to 13 ounces. Beyond the capacities, overflow leakages would occur. However, in one dog overflow never did occur. In this dog the ileal urethra was 8 inches long, longer than in any of our other dogs. Catheterization was usually done twice daily. The nonprotein nitrogen rose acutely following transplantation of the ureters to the new bladder, which was usually done as a second stage procedure; then gradually the nonprotein nitrogen values fell over a period of several months to levels just above that of the preoperative state. The nonprotein nitrogen of one dog fell to 26 on once daily catheterization. This dog was continent up to 13 ounces and beyond this overflow occurred. Necropsy revealed some stricturing of the ureters in most cases with varying effects on the upper urinary tracts. The mucosa of the new bladders was everywhere intact.

These experiments convinced us that a continent substitute bladder could be made in this way. The best results were obtained in those dogs with the largest new bladders and the longest ileal urethras.

Our results, plus those of other investigators show that toxic reabsorption of urine from the cecum and ascending colon need not be feared if an adequate amount of urine is completely discharged from the body daily.

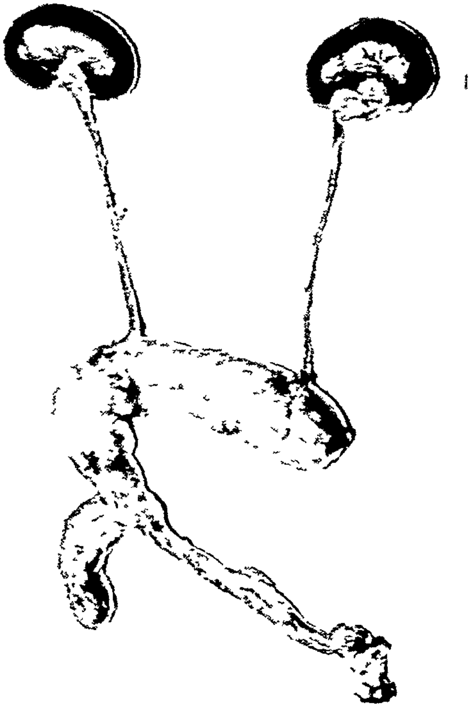

FIG 1. Necropsy specimen of dog 8. Substitute bladder with ileum, appendix and transplanted ureters, which are essentially normal.

Necropsy specimen of dog 8 shows substitute bladder with essentially normal ureters and kidneys (fig. 1).

One reported human case lived 15 years after implantation of the ureters to the isolated cecum with the appendix serving as the external fistula. At necropsy the mucosa of the cecum had lost all glandular elements and resembled that of the true urinary bladder.

To date 4 patients have been operated upon. The construction of the bladder and ureteral transplants were all done as one stage.

Case 1 was a man with a recurrent pararectal sarcoma having had a combined abdominoperineal resection of the rectum elsewhere. At perineal exploration the main tumor mass was found and removed, with the lower end of the sacrum, but several nodules of tumor were seen invading the prostate. Accordingly, in October 1949, a new bladder was formed as described and 2 weeks later the entire bladder and prostate were removed from below. The patient tolerated these procedures very well. An excretory urogram 4 weeks postoperative showed moderate bilateral hydronephrosis (fig. 2). A cystoscope was passed to the new bladder and both ureteral orifices were visualized. At no time were his nonprotein nitrogen, CO_2, and blood chlorides abnormal. Later urograms showed much less dilatation. When last heard from recently he was comfortable and doing well. He catheterizes himself about every 4 hours. In subsequent patients we have obtained greater capacity by making the bladder larger.

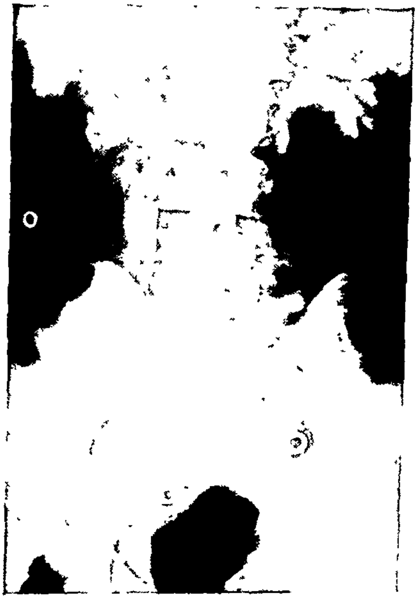

FIG. 2. Excretory urogram 4 weeks postoperative. Moderate bilateral hydronephrosis. Preoperative film not obtained, but at operation left ureter moderately dilated.

Case 2 was a man with an infiltrating carcinoma of the bladder. Following the operation, in which the pathological process was not removed, he rapidly went downhill and died on the seventh postoperative day. Necropsy revealed a massive peritonitis due to necrosis of the turned in end of the new bladder.

Case 3 was a man with a large carcinoma of the prostate which seemed attached to the rectum but with no demonstrable metastases (fig. 3, *A*). In December 1949, a new bladder was formed and he was discharged from the hospital on estrogen therapy to recuperate at home prior to the secondary radical removal of the prostate, bladder and possibly rectum. Four weeks postoperative the nonprotein nitrogen, CO_2, and blood chlorides were normal. An excretory urogram showed a moderate bilateral hydronephrosis. He was perfectly comfortable (fig. 3, *B*). A cystoscope was passed to the new bladder and both ureteral orifices were visualized. Retrograde cystogram of the new bladder showed no ureteral reflux (fig. 3, *C*).

In February 1950, he was re-operated on but metastases were found to lymph nodes and he was closed. Orchiectomy was done. An excretory urogram 4 months postoperative (fig. 3, *D*) showed an essentially normal picture bilaterally and

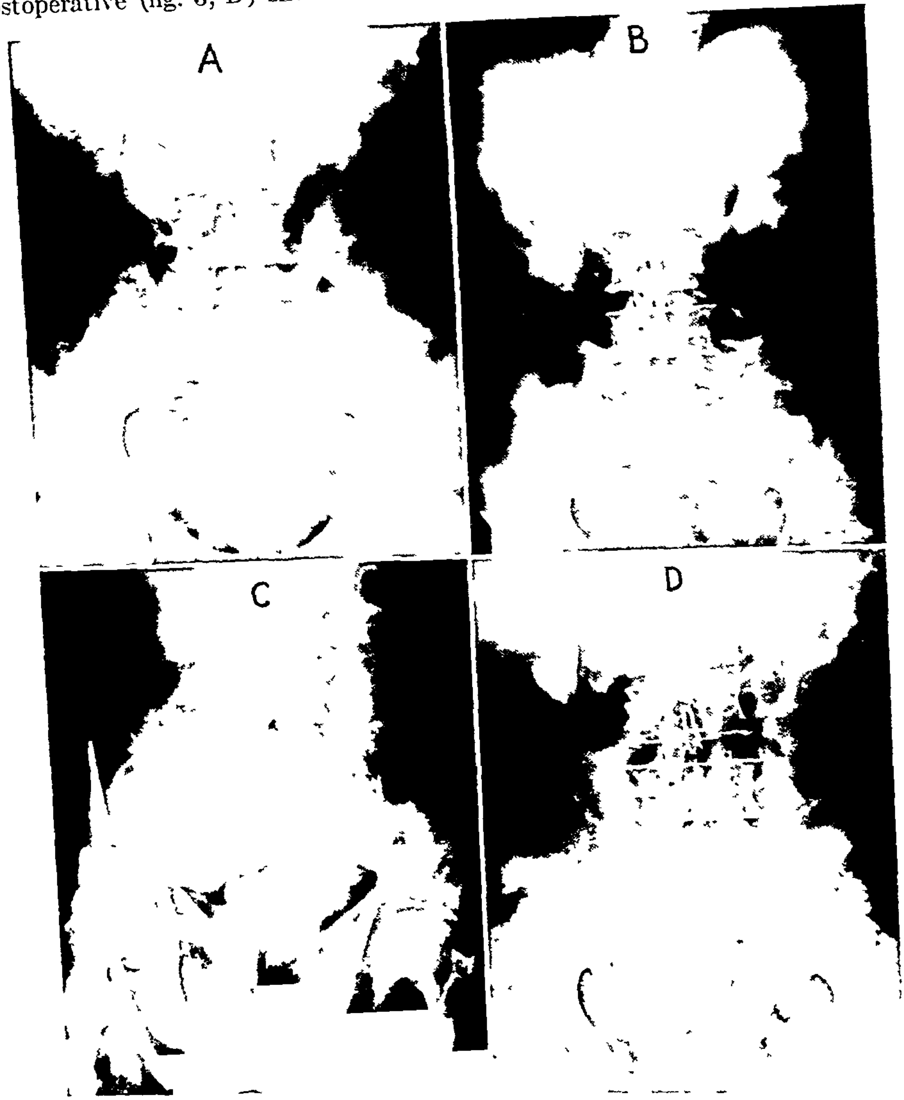

FIG 3 *A*, preoperative excretory urogram. *B*, same case as *A*. Excretory urogram 1 month postoperative Mild dilatation of upper urinary tract. *C*, same case as *A*. Retrograde cystogram, 300 cc contrast medium. Absence of ureteral reflux, competent ureterocecal valve in substitute bladder. *D*, same case as *A*. Excretory urogram 4 months postoperative. Essentially normal upper urinary tract.

also at this time the nonprotein nitrogen, CO_2, and blood chlorides were normal. In May 1950 this patient was comfortable from a urinary standpoint although having considerable pain from metastases. He catheterizes himself every 5 to 6 hours to prevent leakage and has a bladder capacity of about 300 cc.

Case 4 was a man with extremely severe bladder symptoms due to an infiltrating carcinoma of the bladder (fig. 4, *A*). Following the operation he was

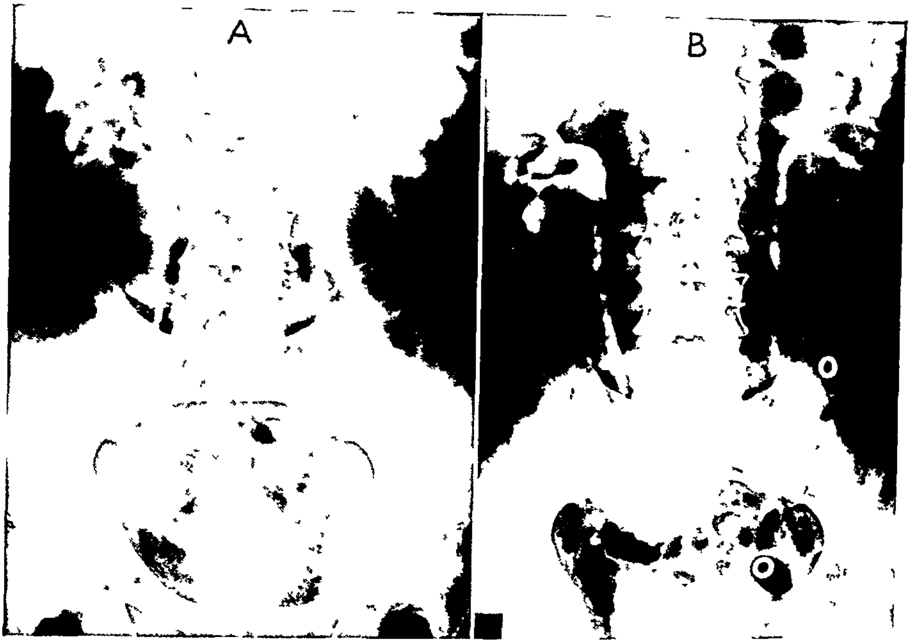

FIG. 4. Case 4. *A*, preoperative excretory urogram. Infiltrating carcinoma of bladder. *B*, excretory urogram 3 weeks postoperative. Note absence of former kinking of left ureter.

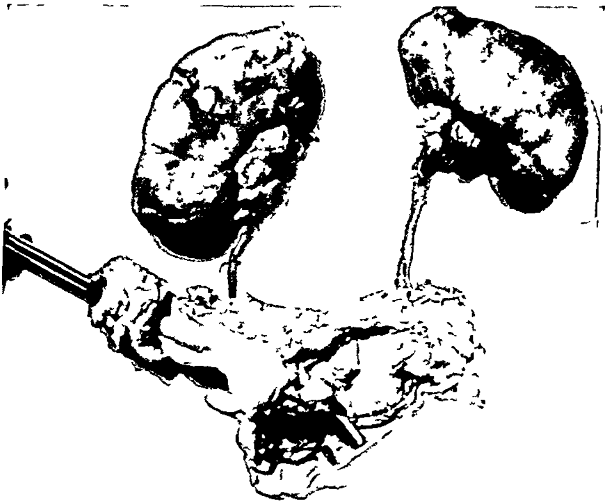

FIG. 5. Case 4. Necropsy specimen of substitute bladder with cystoscope passed through ileum with ureteral catheters in ureters, which are normal size.

completely comfortable and was soon up and around. Excretory urograms 3 weeks postoperative showed much less dilation and kinking of the left ureter, which at operation was dilated about 8 to 10 times normal size and filled with purulent urine (fig. 4, *B*). Just as we planned to complete the pelvic surgery proctocystectomy if necessary. He developed an abscess about the old bladder, went gradually downhill and died. The new bladder functioned perfectly until the patient's death. At necropsy both ureters were essentially normal in size, contrasted with their dilated state preoperatively. Figure 5 shows the substitute bladder at post-mortem with a cystoscope in the ileum and catheters in the ureters 6 weeks postoperative. Note the normal appearance of the ureters. The cause of death was advanced infiltrating carcinoma of the bladder with septicemia and multiple lung abscesses.

SUMMARY

A procedure for the formation of a continent substitute bladder has been presented. This arrangement has certain advantages:

1) There is no contamination by the fecal stream.

2) The ureteral anastomoses are easily made and can be covered by peritoneum.

3) A cystoscope can be passed to the new bladder and the ureteral orifices dilated or otherwise treated if need be.

4) A device is not necessary to prevent leakage.

5) There is no limitation of radical surgery when dealing with malignancy.

In our animal experiments and in the follow-up study of our human patients we have encountered no real contraindication to this procedure. Some may believe that it is too involved technically but familiarity should overcome this, aided by modern preoperative preparation and the various available measures of support during operation. As Appleby has recently said: "The current trend in the treatment of carcinoma is toward gargantuan efforts of extirpative surgery. Something more than a blind response to prevailing tradition is required; the patients should no longer be subjected to standard operations but the operation should be fitted to their unusual needs."

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REFERENCES

Appleby, L. H.: Proctocystectomy. Am. J. Surg., 79: 57–60, 1950.
Bisgard, J. D.: Substitution of urinary bladder with isolated segment of sigmoid colon. Arch. Surg., 59: 588–596, 1949.
Cole, W. H., et al.: Strictures of common duct. Ann. Surg., 128: 332–347, 1948.
Gilchrist, R. K., Merricks, J. W., Hamlin, Howard H., and Rieger, I. T.: Construction of a substitute bladder and urethra. Surg., Gynec. and Obst., 90: 752–760, 1950.
Mann, F. C., and Bollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract. Ann. Surg., 93: 794–797, 1931.
Pearse, H.: An experimental study of antiperistaltic jejunal loops. Ann. Surg., 129: 57–64, 1949.
Rubin, S.: The formation of an artificial urinary bladder with perfect continence: an experimental study. J. Urol., 60: 874–906, 1948.

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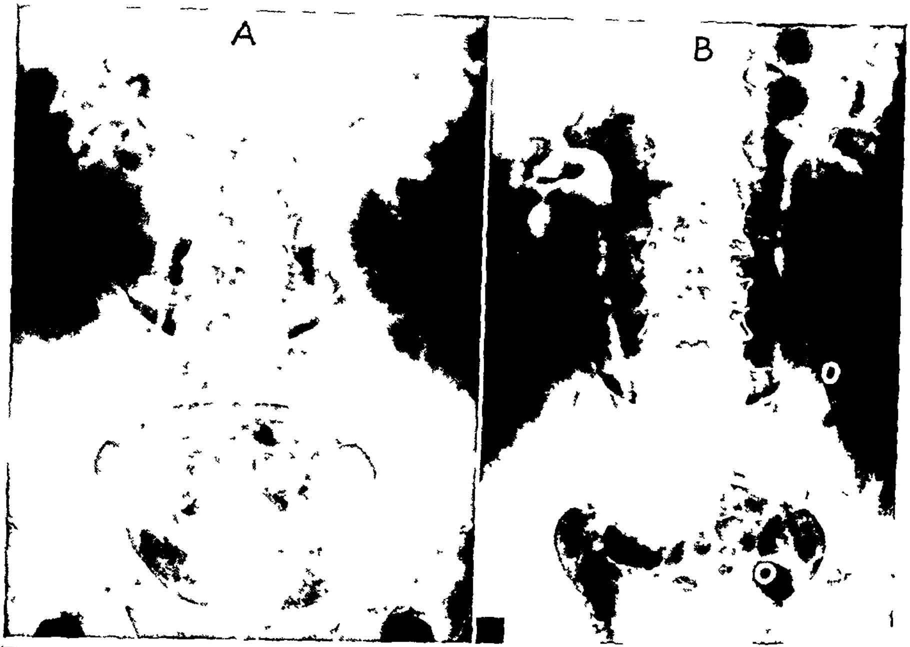

FIG. 4. Case 4. *A*, preoperative excretory urogram. Infiltrating carcinoma of bladder *B*, excretory urogram 3 weeks postoperative. Note absence of former kinking of left ureter

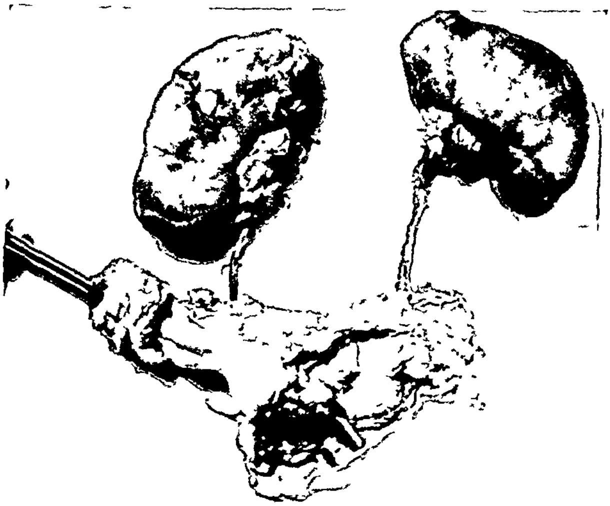

FIG. 5. Case 4. Necropsy specimen of substitute bladder with cystoscope passed through ileum with ureteral catheters in ureters, which are normal size.

two stages with an interval of from 45–70 days in order to obtain an aseptic condition of the cecum. With the currently available antibiotics, this is no longer necessary.

In our dogs, an artificial sigmoid bladder is made in one stage; the urine cultures up to 2 years postoperative have been negative and the upper urinary tract of a dog sacrificed at this stage showed no evidence of pyelonephritis or obstruction; and culture of the pelvis was sterile.

Recently an artificial sigmoid bladder was made for a human patient, and this will soon reach publication.

Two other points I think are worth stating:

First, and of great importance is that such a procedure as herein presented would be excellent for cases of urinary incontinence wherein the external sphincters have been destroyed, as in exstrophy, and a good measure of urinary control and comfort can be attained; and secondly, when a ureter is short or involved in an extensive pathological process. The short ureter can be sufficiently mobilized to permit its implantation in a high and mobile ascending colon.

Certainly in the total cystectomy procedures advocated by Marshall with the formation of a wet colostomy, this type of urinary reservoir and ureteral disposal would be ideal.

DR. JAMES W. MERRICKS (Chicago, Ill.): I hope that Dr. Rubin will continue his excellent work and that others will be stimulated, as we were, to study this problem.

Dr. Rubin stressed the matter of incontinence. The new bladder must be made large enough. The ileum should be brought to the skin through a small stab wound near the rectus border laterally, and rather high. It takes some weeks for control to develop and in most it becomes satisfactory, one fellow can hold up to 700 cc without spilling.

As for indications for the procedure, we were primarily interested in the problem of putting the ureters in a practical place that would hold the urine when it was necessary to do radical pelvic surgery in which there was little chance of preserving the urinary sphincter. Often in this type of patient, the rectosigmoid must be removed; thus the sigmoid is unavailable for bladder substitution. I wish to again thank Dr. Rubin for his discussion, and express the hope that further work will be done on this pressing problem.

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DISCUSSION

DR. SEYMOUR W. RUBIN (Baltimore, Md.): Drs. Merricks, Gilchrist, Hamlin and Reiger are to be commended on their lucid presentation of a daring and very necessary surgical approach to a problem that so far has been very trying.

The main problem in radical surgery of the bladder is the problem of the transplanted ureter, for obstruction at the ureteral implantation and contamination from the fecal pool result in renal destruction.

Many different techniques have been devised in an attempt to avoid obstruction at the site of ureteral implantation with some measure of success, but only recently have we dared again to clear up this contaminated area. The introduction of the sulfonamides and antibiotics and the exclusion of the fecal stream from the urinary reservoir have been recent and agile strides in the direction of asepsis.

Another procedure for the formation of an artificial bladder is very welcome and many more attempts at such procedures are needed for the proper evaluation of our results.

The utilization of the cecum as a reservoir has some drawbacks. Nitrogenous products are more readily absorbed in this area than in the sigmoid as recently demonstrated by Boyce, and an exhibit by Drs. Boyce and Lowsley clearly demonstrates these points. However, frequent emptying of the cecal reservoir does prevent excessive absorption and is compatible with life as evidenced in Dr. Merricks' cases.

A serious drawback is the necessity of repeated catheterization which must continue for lifetime. This procedure in itself works to defeat the very purpose of the operation: the formation of an aseptic reservoir for urine. Certainly, repeated and inexpert catheterization will invariably lead to infection and pyelonephritis with subsequent destructive renal changes.

A third drawback to this procedure is the absence of voluntary control of urination. These patients will be incontinent, an overflow incontinence, if they do not catheterize themselves every 4 hours regardless of the convenience of the environment or the time of the night.

The formation of an artificial sigmoid bladder with anastomosis of the "bladder" neck to the urethra can overcome such objections and enable the patient to live in a normal environment and still retain the benefits of an aseptic urinary reservoir. Voluntary control through a normal urethral sphincter permits these patients to live a normal "urinary life."

However, the best results will be evident as time passes.

The case cited of a 15 year survival with Triana's procedure is noteworthy. The mucosal metaplasia from glandular to urinary type epithelium has not as yet been substantiated in our dog sacrificed at 2 years. The sigmoid bladder mucosa was unmistakably colon mucosa with an abundance of goblet cells.

Recently (1946) Cortes reported Triana's procedure on three women with vesicovaginal fistulas with excellent results. This procedure was performed in the urethral wall. As soon as a small segment of the diaphragm was divided, the cut edges of the urethral mucous membrane were immediately brought together with an interrupted suture of fine silk, the ends of which were left long. The incision over the diaphragm was carried along its line of attachment to the urethral canal until it was excised completely. Sutures to approximate the edges of the mucous membrane of the urethra were applied as the excision proceeded. After suturing was complete, the long ends of the silk sutures were threaded

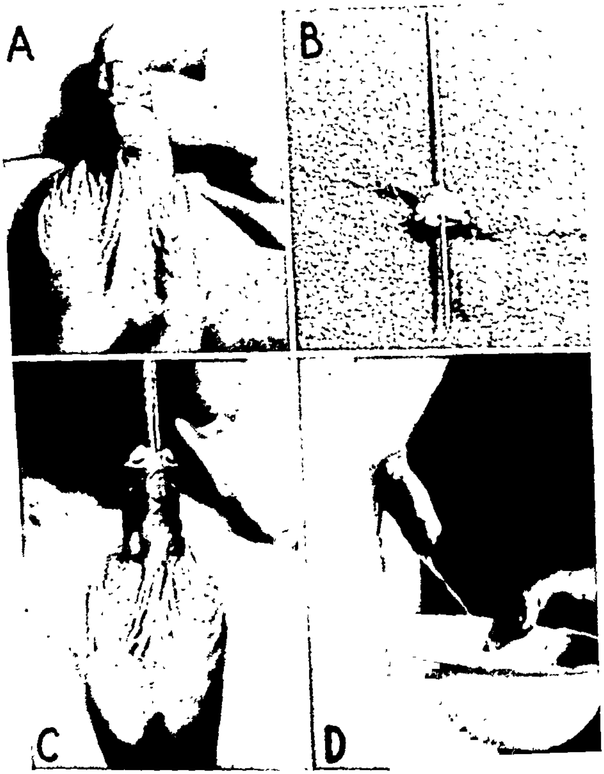

Fig. 1. *A*, preoperative picture showing size and location of fistula. *B*, excised urethral diaphragm with a surgical skin needle passed through its central opening. *C*, postoperative picture showing healed penile incision, and 18 F sound in urethra. *D*, postoperative view showing normal passage of urine during micturition.

through a large needle and brought out of the urethral meatus. With the membrane removed, a 16F sound could be passed into the bladder from the meatus with ease.

Next, a perineal urethrostomy was established through which a 16F Pezzer catheter was inserted into the bladder.

Lastly, the fistula was repaired. With a 14F rubber catheter in the urethra, an elliptical incision was made around and a short distance away from the fistulous opening. The skin was undermined in all directions. Four Young's removable silk mattress sutures were used to invert and close the opening of the

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CONGENITAL DIAPHRAGM AND FISTULA OF PENILE URETHRA

H. C. TSENG

From the Department of Surgery, Peiping Union Medical College Hospital, Peking, China

Congenital valves or diaphragms are not infrequently observed in the posterior urethra,[1] but similar lesions in the penile urethra are rare. Recently a patient with an iris type of diaphragm in the penile urethra associated with a proximal urinary fistula came under my care. Because of the rarity of this anomaly, a brief report of the case is given.

L. T. H., Hospital No. 82139, a boy of 13 years of age, was admitted to the PUMC Hospital on August 8, 1949 because of leakage of urine through a fistula on the ventral surface of the penis since birth. Exact information about the patient previous to the age of 5 years could not be obtained except that the urine came out mainly from the meatus at times by dribbling, while a small portion leaked out from the pin-point fistula on the shaft. At the age of 5, two attempts were made in another hospital to close the fistula; both failed. As a result, the opening of the fistula became very much enlarged. Since that time the urine passed out freely through the fistula, only a few drops appearing at the urethral meatus during the process of micturition.

The patient was well developed and in good health. The general physical findings were normal and examination of the blood and urine revealed nothing of note. The genitalia were of normal size for the patient's age and both testicles were present in the scrotum. On the ventral aspect of the middle of the shaft of the penis was a urethral fistula measuring 6 by 6 mm. in size (fig. 1, *A*). The urethral mucosa could be clearly seen through the opening. The tissues surrounding the fistula were soft and not scarred. The urethral meatus was patent but was situated at the ventral aspect of the glans near the frenulum. A 16F metal sound introduced through the meatus met obstruction just distal to the fistulous opening, although a probe could be passed through. The obstructing membrane was soft and resilient. With pressure exerted on the sound, a diaphragm-like structure could be seen through the fistulous opening. At the center of the diaphragm was a small hole 1–2 mm. in size (fig. 2, *I* and *II*). The caliber of the urethra distal to the diaphragm was normal. This was confirmed by urethrography after injection of sodium iodide solution through the urethral meatus. A sound could be passed into the bladder from the fistula without difficulty.

Excision of the urethral diaphragm and closure of the fistula were carried out under spinal anesthesia on August 15, 1949. The operative procedure is illustrated in figure 2, *II* to *VIII*. With the patient in lithotomy position, a 16F sound was introduced into the urethra from the meatus until it pushed the diaphragm proximally so that it was exposed through the fistula. The diaphragm was incised circumferentially over the sound along its attachment to

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[1] Shih, H. E. and Char, G. Y.: Chin. M. J. 52: 19, 1937.

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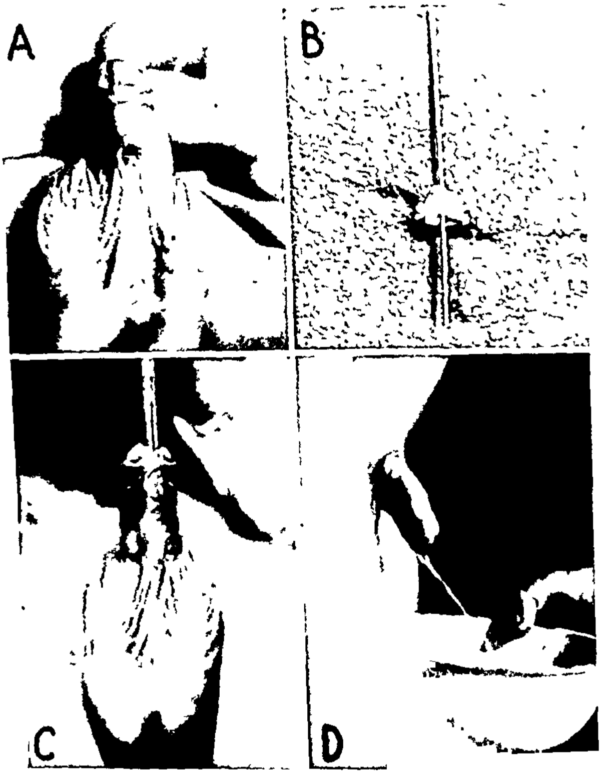

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[1] Shih, H. E. and Char, G. Y.: Chin. M. J. 52: 19, 1937.

The patient was seen again 9 days after his discharge from the hospital. He could urinate freely and the urethrostomy wound had healed. One month later, he remained free from symptoms. Sounding (18F) revealed slight narrowing at the previous site of the diaphragm (fig. 1, *C* and *D*). His condition remained the same, when he was last seen on November 5, 1949.

Pathological report: The diaphragm was disc-shaped; it had a diameter of 6–7 mm. and was 1.5 mm. thick. In its center was an opening about 1–2 mm. across (fig. 1, *B*). Microscopically, the diaphragm consisted of fibro-areolar tissue containing glandular structures, and its surfaces were lined by squamous epithelium. Excessive scar tissue was not present.

DISCUSSION

A perusal of the literature of the last 30 years reveals only a few reports of obstructive lesions in the anterior urethra. Birdsall in 1929 reported an instance of a complete septum 3 mm. wide and $\frac{3}{4}$ of an inch from the meatus observed in an infant 6 hours old.[2] The patient recovered following external urethrotomy and excision of the lesion. Jablonsky in 1933 observed a membranous septum across the upper wall of the urethra at the penoscrotal junction in a man aged 34 years who had no difficulty in urination.[3] He states that Demitrijeff in 1929 encountered a case of a similar septum located at the bulbous urethra. Dourmashkin in 1943 reported 1 case of obstruction of the cavernous urethra among a series of fifty-five living infants seen because of completely obstructive lesions of the urethra.[4] The combination of an anterior urethral diaphragm and an urinary fistula, to our knowledge, has not been recorded.

Undoubtedly, the diaphragm was chiefly responsible for the failure of the attempts at operative closure of the fistula. The enlargement of the urinary fistula following the operative procedures was in fact beneficial to the patient, as it relieved the obstruction to the urinary flow at a comparatively early age and thus prevented damage to the upper urinary tract.

The presence of the large fistula also facilitated the detection of the diaphragm and its removal. However, the diagnosis should not have been difficult even if a fistula had not been present. The history of difficulty in urination would have called attention to the presence of an obstructive lesion. The site of obstruction could have been accurately located by the introduction of a catheter or a sound. A negative history of injury or inflammation and the resilient nature of the diaphragm should have ruled out cicatricial stricture. Endoscopy and cysto-urethrography would have confirmed the diagnosis.

Neither was the presence of the fistula essential for the operative treatment

[2] Birdsall, J. C.: J. Urol. **22:** 438, 1929.

[3] Jablonsky, S.: Ztschr. f. Urol. **27:** 694, 1933.

[4] Dourmashkin, R. L.: J. Urol. **50:** 747, 1943.

fistula. The skin incision was closed with interrupted sutures of fine silk. The primary incision was made in such a way that following closure these two suture lines did not fall in the same vertical plane but overlapped each other. All bleeders were controlled by clamping only; no sutures or ligatures were left buried in the wound.

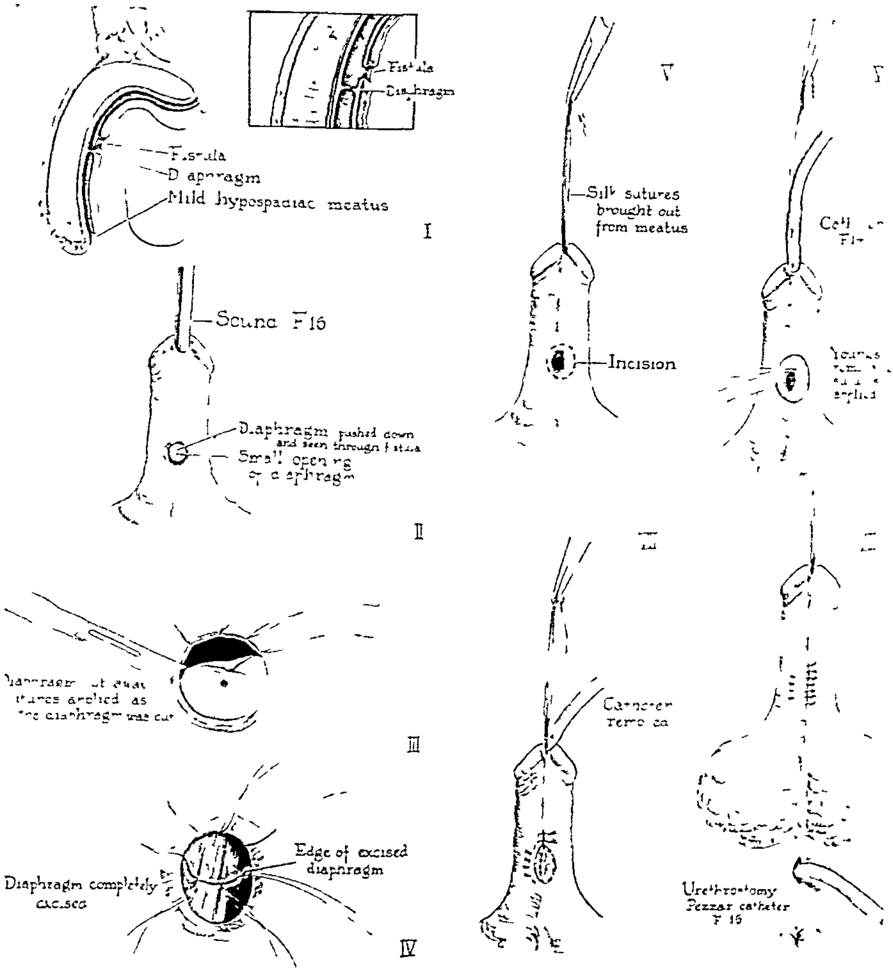
Fistula
Diaphragm
Fistula
Diaphragm
Mild hypospadiac meatus
I
Sound F16
Diaphragm pushed down and seen through fistula
Small opening of diaphragm
II
Diaphragm cut away
Sutures applied as the diaphragm was cut
III
Edge of excised diaphragm
Diaphragm completely excised
IV
V
Silk sutures brought out from meatus
Incision
VI
VII
VIII
Urethrostomy Pezzar catheter F 16

Fig. 2. *I*, Diagrammatic representation of lesion *II* to *VIII*, Operative procedures in excision of diaphragm and closure of fistula.

After the operation, the patient received penicillin intramuscularly in the dosage of 80,000 units every 8 hours for 3 days and 2 gm. of sulfadiazine daily for 8 days. The external penile wound healed per primam, and all sutures were removed by the sixth postoperative day. The long ends of the sutures from inside the urethra were anchored to the lower abdomen by means of adhesive tape and slight tension was exerted on them after the third postoperative day. They came away spontaneously on the eighth postoperative day. Four days later, the urethrostomy catheter was removed, and the patient voided freely

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SURGICAL TREATMENT OF HYPOSPADIAS, ESPECIALLY SCROTAL AND PERINEAL

DAVID M. DAVIS

From the Department of Urology, Jefferson Medical College, Philadelphia, Pa.

The combination of qualities necessary for the surgical treatment of hypospadias is found in comparatively few individuals. One can only say that hurried and ill-considered operations are sure to fail, and that no one should undertake to operate for hypospadias unless he is willing to devote the time and energy necessary for a thorough study of the methods which have proved satisfactory, and to a meticulous performance of the operative procedures. After that he may proceed to invent new and improved methods for himself.

The method to be used in constructing the new urethra should be determined before the first operation, that for straightening the penis, is carried out. The straightening of the corpora and glans is comparatively easy, but since the ventrum of the penis is greatly lengthened thereby, skin must be found to cover the denuded area. If the prepuce is not to be used for the urethral tube, it is very satisfactory for covering the ventrum of the penis, but if it is to be used, other methods are necessary. By extending the ventral incision along the coronary sulcus on both sides of the frenum in the form of a Y and undermining the skin, it has been found possible to pull the lateral parts of the prepuce around to lengthen the covering of the ventrum without shortening the prepuce (fig. 1). This is important if the prepuce is to be used for a tube-flap.

We may then consider the current methods of constructing the urethral tube. I think it is fair to say that the old standard Thiersch-Duplay procedure is definitely outmoded for the penile portion of the repair and should be abandoned. The reason for this is that it superimposes one line of suture on another, so that complete healing almost never occurs, and the usual result is a series of fistulas, large or small, and very difficult to close.

In order to avoid the possibility of multiple fistulas, surgeons for a long time have attempted to create a tunnel within the penis, and line it in some manner with epithelium. For this purpose split thickness skin grafts, full thickness skin grafts, pedicle flaps, free grafts of bladder wall, and even pieces of large veins have been used. Many good results have been obtained, but failure has usually been due to necrosis of the graft.

In my own experience, the Thiersch-Duplay operation was very satisfactory in the scrotal and perineal regions, but the frequent occurrence of fistulas in the penile portion caused me to cast about for a better method for the construction of the penile urethra. Young had formed a tube from preputial skin, leaving the pedicle attached in the region of the coronary sulcus and passing the tube through a tunnel in the glans. These tubes usually underwent necrosis, and the obvious reason was that the blood supply was inadequate. Consideration of the vascular

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Hot Springs, Va., March 23, 1950.

of the diaphragm. It could have been excised with a Young's punch, as in the case of posterior urethral valves, or it might have been removed under direct vision through an urethrotomy, as used by Birdsall. The suturing of the cut edges of the urethral mucous membrane after excision of the diaphragm minimized scar formation and helped to prevent stricture. This fact is more important for lesions in the anterior urethra than for those of the posterior urethra on account of the smaller caliber of the anterior urethral canal. The diversion of the urinary stream by means of a perineal urethrostomy, the avoidance of buried sutures or ligatures, and the use of chemotherapeutic and antibiotic agents helped in securing primary healing of the wound. Postoperative periodic dilatation of the urethra, however, still will be essential to prevent stricture and to conserve the good result obtained.

and the new urethra can immediately be anastomosed with the pre-existing urethra (fig. 3). While it is true that good results can be obtained with free grafts placed in a tunnel, the advantage of the pedicle is that it assures complete viability of the flap in 100 per cent of the cases. The pedicle is cut in about three weeks (fig. 4).

The tube flap method places the new urethral meatus at the tip of the glans, where it belongs. I believe that this point is important, particularly from the psychic and emotional point of view. With such a meatus in a well-straightened penis, both the patient and his parents can feel that the condition is indistinguishable from normal and that not even a remnant of malformation remains. This enables them to forget the whole distressing affair, with its implication of hidden weakness.

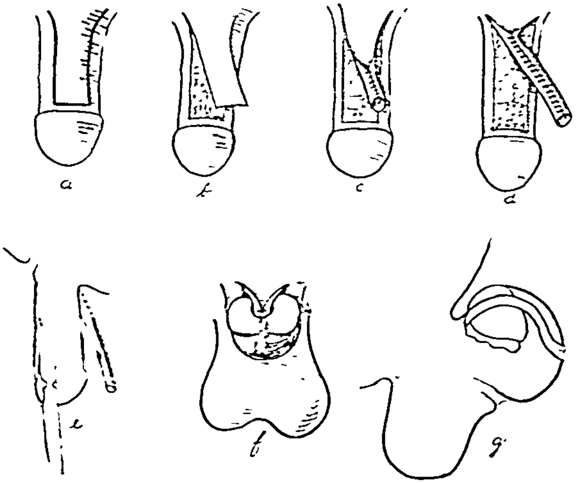

FIG. 2. a, Operation for construction of tube-flap. The flap is outlined on the dorsum of the penis; b, flap raised from dorsal surface of corpora; c, flap sutured into a tube; d, tube completed; e, tunnel made from tip of glans, the same length as the tube-flap; f and g, tube drawn into tunnel, penis bent ventrally to bring tip of glans to base of pedicle of tube-flap.

In any tunnelization method, there can be at the maximum, only one postoperative fistula, namely, at the proximal end of the tunnel. The best method for closing such a fistula is the inversion method, described some years ago.[1] The tract is dissected free, with a little rim of external skin, and pulled inside out, so that it projects into the urethral lumen. This method is successful in at least two thirds of cases on the first attempt, and always on the second or third.

The pedicle tube-flap method has been so uniformly successful that I have not felt impelled to turn to other methods, in spite of the good results reported. There are other considerations which I believe should carry a good deal of weight. With the pedicle tube-flap method, it is often possible to complete the construction of the entire urethra in one operation. It is never necessary for the patient to wear an apparatus of foreign material in the penis for a long time.

[1] Surg., Gynec. & Obst., 71: 790–796, 1940.

system of the penis made it apparent that the arteries supplying blood to the prepuce were on the dorsal surface, near the midline and just beneath the skin, and they coursed from the base of the penis toward its tip. It therefore seemed possible to cut the flap in such a manner that its attachment or pedicle would be at its proximal end instead of at its distal end, and so preserve its blood supply. The attachment was of course at some distance from the tip of the glans, but it was found that the glans could easily be bent or folded back so that its tip reached the area of the attachment, and the whole length of the tube flap could be drawn into the tunnel in the glans (fig. 2). A few trials showed that the blood supply was entirely adequate and that sloughing never occurred. The idea at first was to use the preputial tube-flap only for the glandular part of the urethra, but it soon appeared, not only that the prepuce often furnished quite a long tube, but that, owing to the flexibility of the penis, the flap could be cut along the entire length of the dorsum of the penis, right up to the point at its base where hair follicles began to be present in the skin. It is now customary to make the tube flap as long as possible, measure its length, and then make the penile tunnel the same length as the tube flap. In a surprisingly large number of cases of penoscrotal hypospadias, the tube-flap is easily long enough to reach all the way to the meatus, so that no flap-cutting whatever is necessary on the ventral surface,

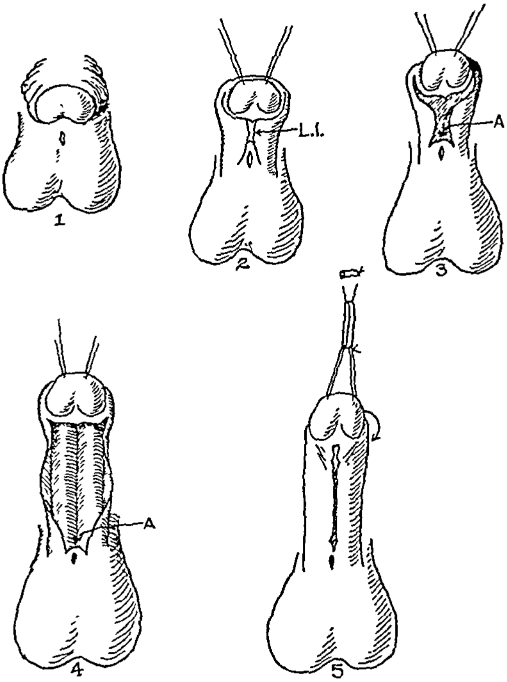

FIG. 1. *1*, *Anterior view of typical penoscrotal hypospadias*; *2*, L.I. is line of incision for straightening operation. Small quadrilateral piece of skin is excised with underlying fibrous band. Horns of incision extend around into loose preputial skin; *3*, edges of incision are undermined; *4*, all fibrous bands and adhesions are removed. Corpora must be completely freed. Urethra is separated from the corpora at *A* for some distance, and all fibrous tissue removed; *5*, preputial skin pulled around penis in direction of arrow, giving plenty of skin for linear ventral closure. Penis held up to abdominal wall by rubber band.

It has been conclusively shown in a number of my patients that a urethra constructed from a full thickness pedicle tube-flap of preputial skin will grow as the penis grows, and the operation can be done at an early age, usually 4 to 6 years. It is my experience that this is extremely important, not only for the sake of the patient, but especially for the sake of the parents, who usually suffer emotionally from the congenital defects of their offspring more than the patients themselves do.

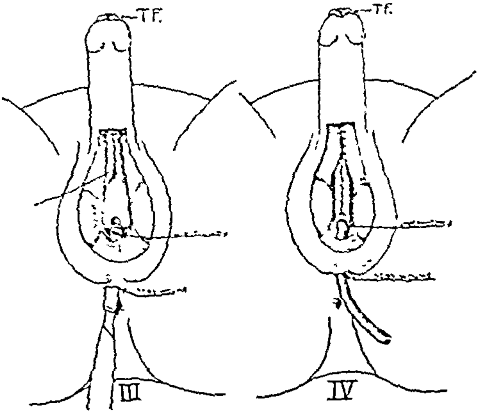

Fig. 6. *III*, Strip of skin being sutured into a tube. Meanwhile a typical tube-flap has been raised from dorsum of penis and drawn into tunnel (T.F.). End-to-end anastomosis between it and the perineal portion of tube. Stab wound made in perineum well posterior to scrotum, tunnel made to a point near urethra. Urethrotomy made just proximal to meatus; *IV*, Perineal part of tube completed and closed over meatus, catheter passed through tunnel and urethrotomy into bladder to divert urine. Closure of scrotal and penile tissues over tube begun.

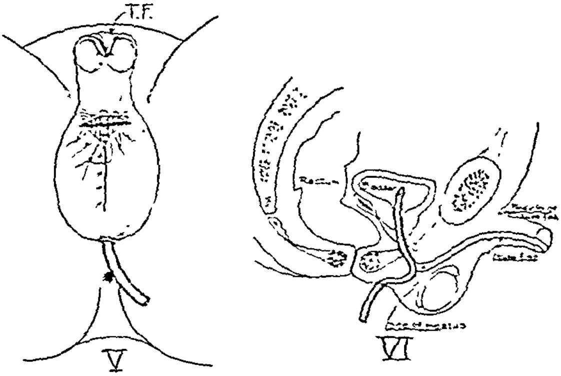

Fig. 7. *V*, Closure of scrotum continued, burying new urethra as deeply as possible. Anterior part of incision closed transversely, to bury anastomosis between perineal part of urethral tube and penile tube-flap as deeply as possible. This pulls penis and scrotum together. Any web formed can be easily divided later. *VI*, Diagrammatic cross section showing situation after operation when pedicle of the tube-flap is divided. Unlined scrotal tunnel heals quickly after the catheter is withdrawn.

The more severe degrees of hypospadias, that is, the scrotal and perineal, appear at first to offer much greater surgical problems. This I believe not to

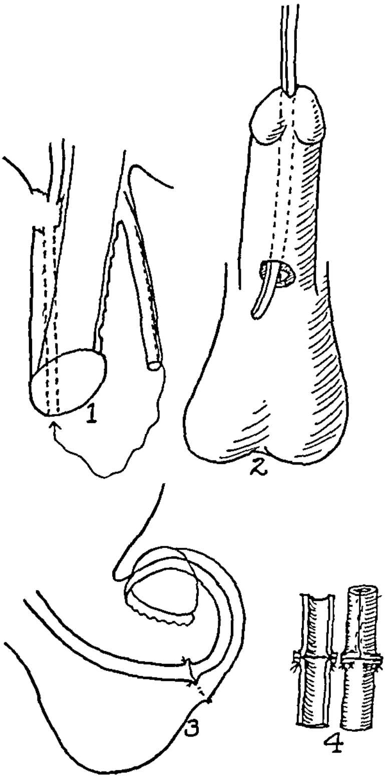

FIG. 3.

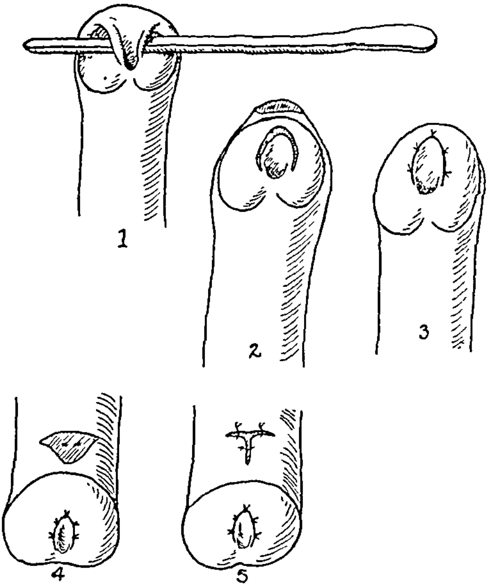

FIG. 4.

FIG. 3. *1*, Manner of making tunnel when tube is long enough to reach meatus. Arrow shows direction in which end of tube is pulled through tunnel. *2*, Curved hemostat passed through tunnel to make sure it is large enough; *3*, Penis bent backward to receive tub flap. Tube sutured to freshened end of urethra. *4*, Manner of anastomosing tube to urethra end-to-end and mucosa-to-mucosa. Subcutaneous tissues are brought together over thi anastomosis, and scrotum drawn up to bury it as deeply as possible.

FIG. 4. *1*, Manner of dividing pedicle of tube-flap. Grooved director is passed beneath pedicle. *2*, After division of pedicle, arteries are ligated. *3*, Cut edges of tube fastened to skin of glans with a few sutures; *4*, Divided pedicle on dorsum of penis. 5, Skin edges loosely approximated with a few sutures.

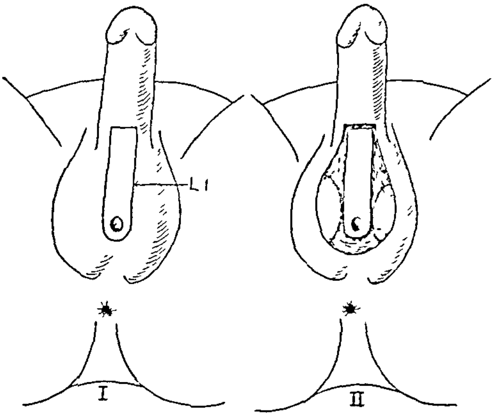

FIG. 5. Operation for midscrotal hypospadias. *I*, Outline (L.I.) of incision. *II*, Skin edges undermined, deep tissues of scrotum, including testes, exposed.

Noting how quickly and easily these fistulas healed, it occurred to me to omit the lining of the posterior limb with skin, and to bring the drainage catheter out through the scrotal and perineal tissues, but buried as deeply as before. This proved to be even more satisfactory, as the perineal fistulas closed spontaneously after the removal of the catheter (figs. 5, 6, 7).

This method has been used in a number of cases of scrotal hypospadias, with uniformly good results. It has not as yet been used in true perineal hypospadias, but I should not hesitate to attempt it. Two cases of perineal hypospadias are illustrated in this paper (fig. 8). In both of these the usual procedure of suprapubic cystostomy was used for diversion of the urine. The results were entirely satisfactory in both, but there is no doubt that suprapubic drainage adds greatly to the discomforts of the patient. If more than one operation is necessary for the urethral construction, one must either maintain the suprapubic drain for a long time, or reinsert it at each operation, a procedure which grows more difficult with each repetition.

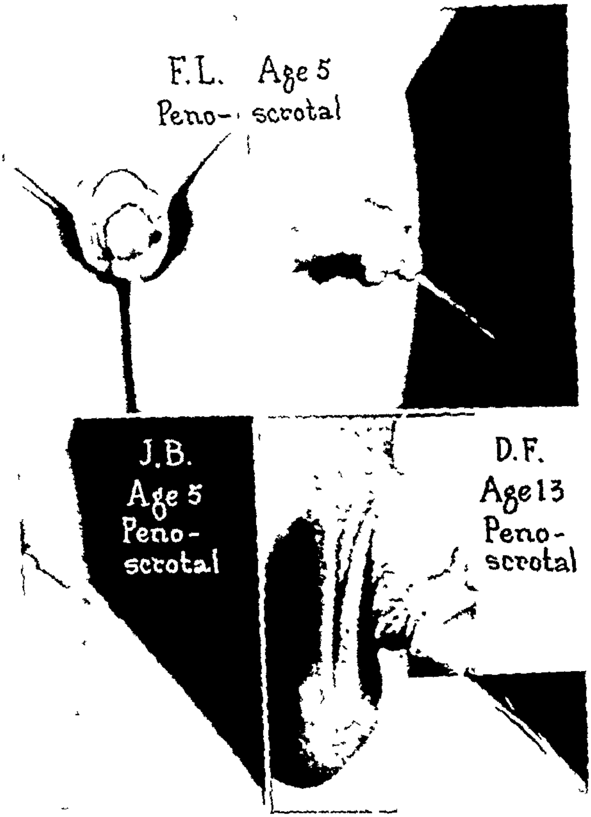

FIG. 9. Final results in 3 typical cases of penoscrotal hypospadias. Note straight penis, normal-appearing glans, and straight, strong urinary stream.

Urinary drainage tubes or catheters, of whatever sort, must be watched carefully for sanding, and if it occurs, irrigated frequently, with acid solutions, be the case. The reason for this is that the new urethra can be buried deep within the tissues of the perineum and scrotum, which makes fistula formation unlikely, regardless of the method of plastic reconstruction used. The tendency toward healing is in fact so great that we now do not hesitate to leave a fistulous tract in this region, for the diversion of urine, and find that it heals spontaneously after the withdrawal of the drainage catheter.

Some years ago a method was devised to obviate the necessity for suprapubic diversion of urine in scrotal hypospadias. The scrotal part of the urethra was made by the Thiersch-Duplay method, using the strip of hairless skin in the midline. The Thiersch-Duplay reconstruction was continued posteriorly, past the urethral orifice and well into the perineal region. This produced a T shaped urethra, and through its posterior limb a catheter was brought from the bladder to divert the urine. All of the scrotal and perineal portions of the urethra were then buried very deeply by suturing the scrotal halves together over them with many layers of fine catgut sutures. The results were excellent.[2] The posterior limb of the new urethra of course remained patent, being lined with skin. At a later date this skin lining was excised, and the resulting fistula closed quickly.

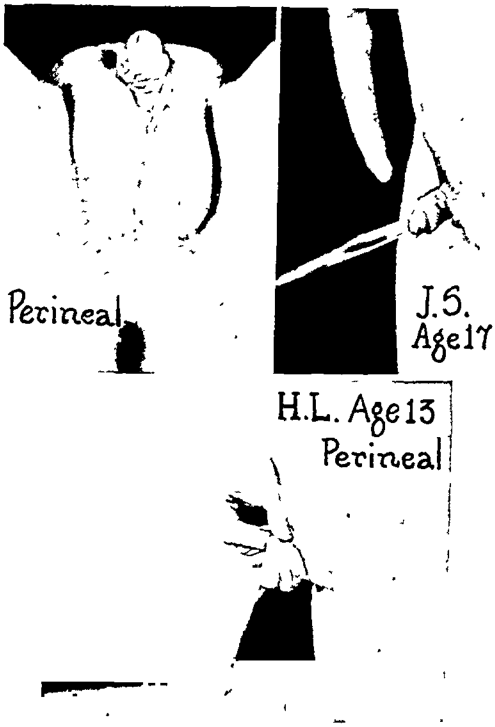

FIG. 8. Final results in 2 cases of perineal hypospadias. Upper row, left panel, case 1, J. S. Scar just below posterior edge of the scrotum marks site of original meatus. Patient now 24 years old, and is married. Urethra admits a 24F instrument easily. Lower photograph, case 2, H. L. Case was unusual in that penis was large, and was buried beneath perineal skin, except a bifid glans which overhung meatus just in front of anus. Result is satisfactory in every respect. Patient now 19 years old.

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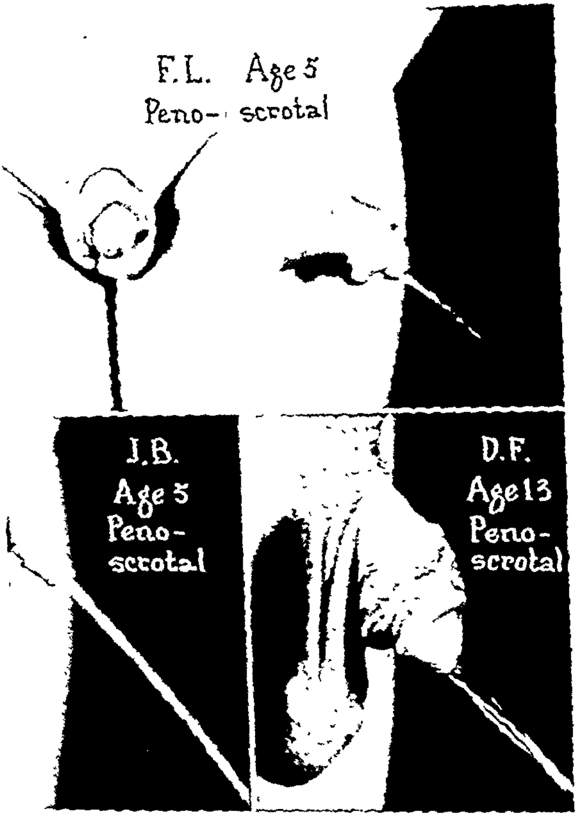
[2] J. Urol., 52: 340, 1944.

Noting how quickly and easily these fistulas healed, it occurred to me to omit the lining of the posterior limb with skin, and to bring the drainage catheter out through the scrotal and perineal tissues, but buried as deeply as before. This proved to be even more satisfactory, as the perineal fistulas closed spontaneously after the removal of the catheter (figs. 5, 6, 7).

This method has been used in a number of cases of scrotal hypospadias, with uniformly good results. It has not as yet been used in true perineal hypospadias, but I should not hesitate to attempt it. Two cases of perineal hypospadias are illustrated in this paper (fig. 8). In both of these the usual procedure of suprapubic cystostomy was used for diversion of the urine. The results were entirely satisfactory in both, but there is no doubt that suprapubic drainage adds greatly to the discomforts of the patient. If more than one operation is necessary for the urethral construction, one must either maintain the suprapubic drain for a long time, or reinsert it at each operation, a procedure which grows more difficult with each repetition.



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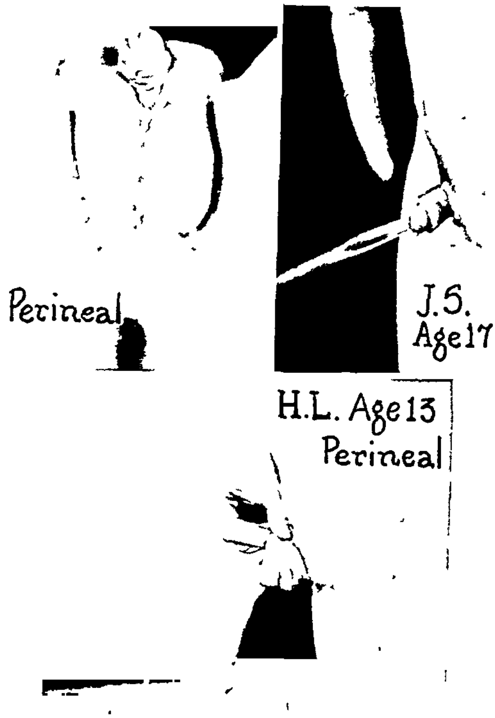

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METHOD AND RHYTHM IN TRANSURETHRAL PROSTATIC RESECTION

ROGER W. BARNES

From the Department of Surgery (Urology) College of Medical Evangelists, School of Medicine, Los Angeles, Calif.

The surgeon must follow a definite sequence of maneuvers and develop rhythm and coordination of movements in order to satisfactorily remove the large prostate gland by transurethral resection. The random removal of pieces of tissue, first on one side, then on the other, or a piece from the bladder neck, followed by one from the apex, is not conducive to efficient and adequate prostatectomy by the endoscopic approach.

There are several methods used by different operators. In the one used by Nesbit, Creevy, and others, the resection is begun at the ventral portion of the bladder neck where the capsule is closest to the urethral mucosa. Bladder neck fibers and capsule are exposed by removing tissue slightly to one side of the midline. Then successive pieces are resected lateralward, downward, and medialward, exposing capsule each time and making a deep groove toward the dorsal midline, thus freeing or "enucleating" the intravesical portion of the lateral lobe from the capsule. This partially enucleated tissue mass is then rapidly cut up with the resectoscope loop into pieces small enough to be evacuated through the sheath. If the prostatic urethra is long, the apical portion on one side is then removed in the same way, and when the bleeding is controlled, the opposite side is resected by the same method.

The advantage of this method is that the major portion of the blood supply to the gland is controlled early by exposing and fulgurating the bleeders at the bladder neck. Thus the bulk of tissue can be removed rapidly with minimal hemorrhage. One of the chief disadvantages is the difficulty of proper orientation. A large mass of partially excised tissue filling the urethra tends to obstruct vision and to cover landmarks. The operator may not be sure whether the resectoscope is in the groove near the capsule or in the urethra with the mass of tissue between it and the capsule. Early exposure of the capsule also increases the danger of perforation early in the course of the operation, resulting in greater danger of extravasation.

A method which I prefer is to begin the resection at the dorsal portion of the bladder neck. If there is an intravesical middle lobe, this is removed first (fig. 1). The loop is placed over the edge of the prostatic border at the point where the projecting prostate is most prominent, and a short excursion of the loop is made. The resectoscope is then rotated slightly and the inner end moved to a slightly more lateral position so that the next piece is removed to the side of the first section rather than deep to it (fig. 2, *a*). The maneuver is repeated until the lateral margin of the middle lobe is reached, then the rotation of the resectoscope

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such as Suby's solution, or solution G. Antibiotics undoubtedly increase the incidence of primary healing. Of late months, I have been irrigating the wounds, just before closure, with bacitracin solution, with apparently good results (fig. 9).

In conclusion, I would like to say that I believe the time has arrived to state that the surgical repair of hypospadias is no longer dubious, unreliable, or even extremely difficult. If tried and proven methods are scrupulously followed, a good result should be obtained in every case. Anything less than this suggests that the surgeon is not temperamentally fitted for this kind of surgery.

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and the movement of its inner end are reversed so that the next deeper layer of tissue is resected and the pieces removed consecutively back again across the middle lobe to the starting point. This is continued back and forth until bladder neck fibers are exposed and all of the lobe has been removed. After the middle lobe has been resected in this manner, the bleeders at the exposed bladder neck are fulgurated, and the intravesical portion of one lateral lobe, preferably the larger one if there is any difference, is removed by similar maneuvers. The first piece is resected at the dorsal edge of the lateral lobe, which, in cases in which there is no middle lobe, is the six o'clock position. Consecutive pieces are then removed from this point around the lateral prostatic border to the twelve o'clock position, then back down again for a deeper layer (fig. 2, *b*). This is continued

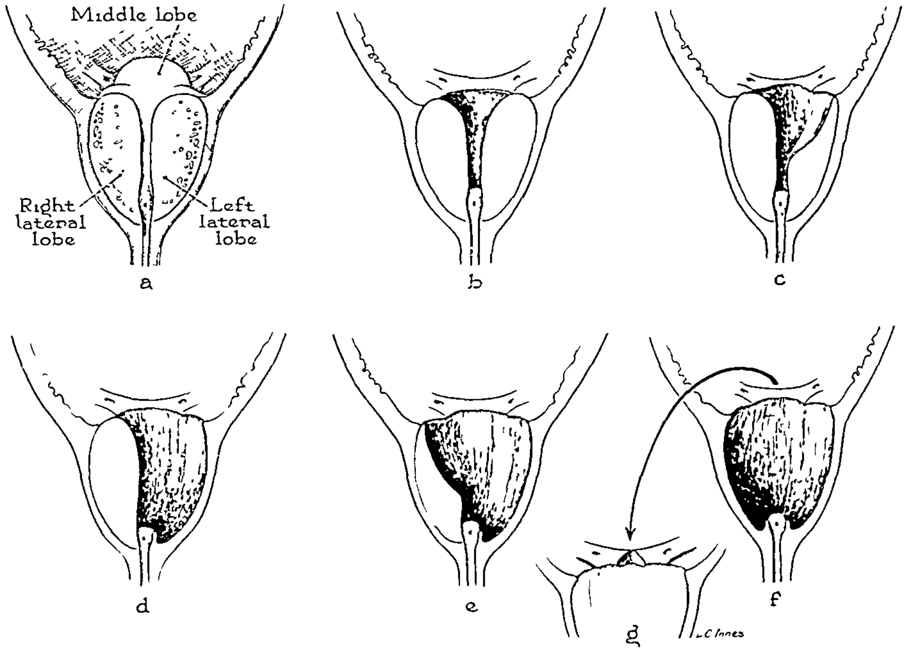

FIG. 1. One section of prostate is completely removed before another section is started. *a*, Horizontal view before operation is begun. *b*, Middle lobe has been removed. *c*, Middle and intravesical left lateral lobes removed. *d*, Middle and entire left lateral lobes removed. *e*, Intra-urethral right lateral lobe only is left. *f*, All of prostate has been removed. *g*, Trigone incised.

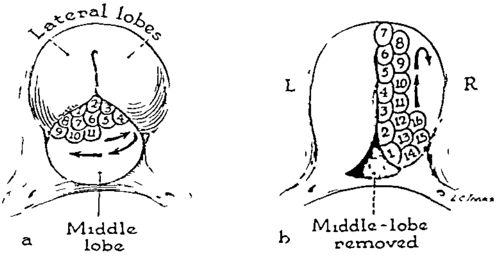

FIG. 2. Transvesical view of prostate being resected showing sequence for removal of pieces of tissue. *a*, Removal of middle lobe. *b*, Removal of lateral lobe. 1, 2, 3 etc. indicate order in which pieces are removed.

until all of the intravesical lateral lobe has been removed and the bladder neck fibers are all exposed on that side; then the bleeders at the bladder neck are fulgurated.

The chief advantage of beginning the series of the loop excursions at the dorsal portion of the bladder neck rather than at its ventral portion is that there are a greater number of easily identifiable landmarks dorsally. The trigone and ureteral orifices in the bladder, and the verumontanum in the urethra are aids in orientation and in determining the inner and the outer limitations of the resection. After the operator becomes orientated and begins removing the consecutive series of pieces, it is very important to keep the resectoscope in the same relative in and out position. If this is done, orientation will not be necessary again until after the irrigating fluid is emptied from the bladder and the removal of another series of pieces is begun.

After the intravesical lateral lobe on one side has been removed, the resectoscope is drawn out into the prostatic urethra and the verumontanum identified. The intra-urethral lateral lobe is then resected in the same manner as the intravesical portion was removed. A consecutive series of pieces is resected beginning at the 6 o'clock position and extending upward on that side to the 12 o'clock position, then down again with a deeper layer returning to the 6 o'clock position. When the operator works rapidly, it is usually possible to complete this maneuver without emptying the bladder. The advantage of removing both the intravesical and intra-urethral portions on one side before starting the other, is that the bleeding at the outer edge of the intravesical portion does not have to be controlled immediately, for this tissue is resected again soon when the intra-urethral segment is removed. After one side has been resected down to the capsule and the bleeding controlled on that side, the other side is resected in the same manner: first the intravesical, then the intra-urethral. Sometimes the urethra is so long that three excursions of the loop are necessary to encompass the entire length of the prostate.

The endoscopic surgeon must develop coordination of movements and rhythm of motion before he is able to remove large prostates rapidly. The foot switch is depressed the instant the loop touches the tissue for the beginning of its excursion, and is released at the exact time the loop enters the sheath at the end of its excursion. The operator's eye must be kept against the ocular end of the resectoscope continuously while pieces are being resected. The most important maneuver is the alternate pressure and release of the inner end of the resectoscope against, and then away from, the tissue being resected. When the loop is in the advanced position ready to begin removing a piece of tissue, the inner end of the resectoscope is pressed against the tissue to be removed by swinging the ocular end of the instrument in the opposite direction, and by depressing the beak with a leverage pressure of the left hand which is holding the instrument. The fingers press the sheath downward while the thumb elevates the ocular end (fig. 3). Thus the inner end of the resectoscope and the loop is swung into the tissue to be removed, and a deeper bite can be engaged by the loop. At the completion of the excursion, when the loop is in the sheath, the opposite maneuver is performed. The inner end of the resectoscope is swung away from the tissue so that the loop can be extended again for the next bite (fig. 4). If this latter maneuver is not carried out, the loop may impinge on the unresected tissue as it is being advanced. Also if the inner end of the sheath is not swung away from the unresected tissue, the last piece removed may be held against the side of the prostatic urethra, thus preventing the piece being washed back into the bladder and resulting in obstruction of view through the lens. This swing into, and then away from, the tissue is developed into a rhythmic series of movements and is coordinated with the action of the footswitch, with the excursion of the loop, and with the eye against the ocular end of the lens. It should be practiced and learned by the trainee before he begins operating on patients.

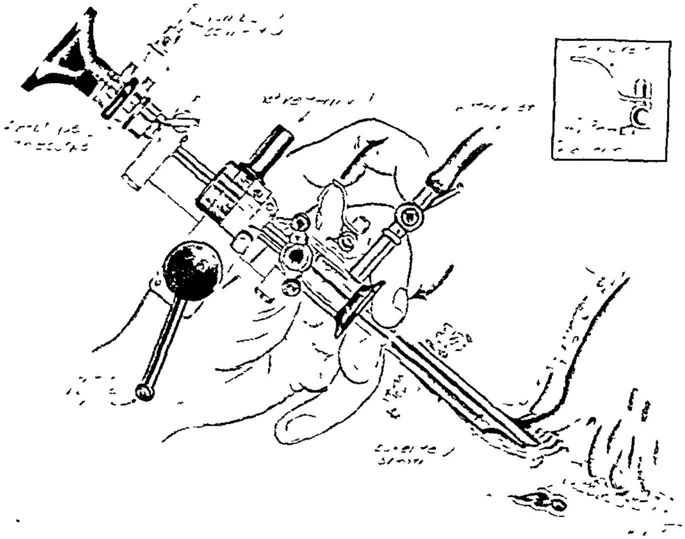

FIG. 3. Leverage pressure of inner end of sheath against tissue to be removed. Arrows indicate direction of pressure while piece of tissue is being resected.

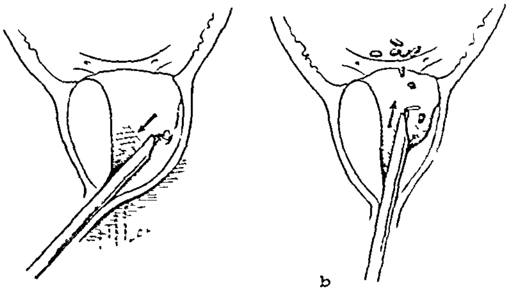

FIG. 4. Inner end of sheath and loop are swung *a*, against tissue while a piece is being resected and *b*, away from tissue while loop is being extended. Arrows indicate direction of movement of loop.

Another maneuver which saves time is the proper manipulation of the water inflow. If this is cut down or turned off whenever a forceful flow is not needed for clear visualization, the bladder does not fill rapidly and it is therefore not necessary to empty the bladder often. Each time the operator stops to empty the bladder, valuable time is consumed. When the inward excursion of the loop is being made, visualization is not necessary, for the loop is buried in the tissue and the piece of tissue being resected is so close to the lens that visualization is not possible. There is therefore at this time no necessity for any water inflow. The water is shut off at the instant the loop is placed to begin the removal of a piece and is turned on again when visualization is necessary to place the loop to remove the next piece. This control of water inflow can be made with the petcock manipulated by the index finger of the left hand, by kinking the inflow tube, by the use of a Timberlake valve or in some other way. It is coordinated with the other maneuvers described previously.

More important than the specific method or technique used is the necessity for the operator to follow the method he uses in a logical sequence of steps, and to develop a rhythm and coordination of movements which will enable him to perform the difficult transurethral prostatic resection rapidly and accurately.

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CONSERVATIVE TREATMENT OF HIGHLY OBSTRUCTIVE CANCER OF THE PROSTATE

R. B. MULLENIX AND R. J. PRENTISS

Surgical relief of severe obstruction due to cancer of the prostate is usually unnecessary. Following the acceptance of estrogenic therapy the authors have gradually widened their application of this treatment to include cases of the most severe obstructions, and the surgical relief of these obstructions is not now frequently used.

Nonobstructive or moderately obstructive prostatic cancer is now treated solely by estrogens almost universally, except in those cases considered suitable for radical prostatectomy. Obstructions of high degree are more frequently treated by primary transurethral resection with secondary estrogenic therapy. In recent years the authors have been impressed with the frequency with which complete urinary retention due to prostatic cancer has been relieved by prolonged catheter drainage and administration of estrogens without resort to prostatic surgery of any type.

Although this review necessarily includes all cases of prostatic malignancy, patients with advanced degrees of bladder neck obstruction are its primary consideration.

One hundred and seventy-nine cases of suspected or proven prostatic cancer have been reviewed and of these 141 were suitable for critical analysis. Thirty-eight cases were discarded for one of the following reasons: the diagnosis of cancer was too uncertain; the patient was moribund at the time of first examination; he was untreated by any means; he was seen too recently for evaluation; or there was no acceptable follow-up information. Because of the difficulty in classifying the many aspects of prostatic malignancy, and since the relief of obstruction is the usual indication for surgical intervention, the element of bladder neck obstruction was selected as the sole criterion in this analysis.

Fifty-five patients had few or moderate symptoms of obstruction and did not exhibit the indications ordinarily required for surgical intervention. These all received estrogenic therapy (castration in some instances) and of this group only 2 have later come to transurethral resection by the authors.

Eight-six patients presented clinical evidence of prostatic cancer and obstruction of a degree sufficient to require surgical treatment according to usual standards. Twenty-four patients were operated on prior to the advent of estrogenic therapy, and were thus deprived of its benefits. Forty-two underwent operation of some type followed by estrogenic therapy and only 3 of these required secondary operation while receiving estrogens at a later date. Patients with secondary obstructions who sought help elsewhere of course cannot be accounted for.

Twenty patients with complete or almost complete bladder neck obstruction were treated with intermittent or indwelling catheter catheterization as required

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and simultaneous intensive estrogen therapy. This usually consisted of 15 mg. of diethylstilbestrol daily for two to four weeks with a later maintenance dose of 3 to 5 mg. per day. All of these patients were in need of surgical relief according to usual standards. Sixteen of these patients became able to void acceptably with residual urine of less than 50 cc after removal of the catheter. Four patients remained totally or significantly obstructed and necessarily became candidates for transurethral resection. The usual period of trial on catheter and estrogens was 30 days although for special reasons one case of 8 months and one of 19 months was included.

Of the 16 patients suffering from pronounced obstruction who responded favorably to estrogenic therapy, none has thus far suffered recurrence of sufficient obstruction to require surgical treatment. Of 97 patients who were treated with estrogens alone or by primary operation with subsequent estrogenic therapy, in only 5 has obstruction sufficient to require surgery, developed.

DISCUSSION

These statistics indicate that even complete obstruction due to prostatic cancer does not usually necessitate surgical intervention for relief. In the authors' practice the resection of recognized carcinoma has become an uncommon operation.

During the period of this study and in reviewing the records, certain additional facts became apparent. Patients with greatly enlarged prostates suggesting associated benign prostatic hypertrophy, and patients with diverticula or other evidence of long-standing obstruction were less likely to experience complete relief from estrogenic therapy alone. It may be wiser to subject some of these patients to transurethral resection when their clinical conditions warrant it rather than to insist on the longer period of strictly conservative treatment. However, it was noted that even for the 30 day period of observation the patients were for the most part showing rapid general improvement and were happy and satisfied with their status. Although this program is prolonged and somewhat uncertain it usually permits treatment on an ambulatory basis at home, avoids the risk, disability and expense of operative treatment, and has usually been welcomed by the patients as a desirable alternative to hospitalization and operation.

The use of estrogenic therapy alone in 20 cases of most severe obstruction was undertaken as the most trying test of this mode of treatment. The favorable response of 75 per cent of these patients with pronounced obstruction suggests that at least 85 to 95 per cent of all cases of radically inoperable prostatic cancer will escape operation entirely.

The great degree of involution or regression seen in some prostatic cancers under estrogenic therapy, in a few instances, has been a cause of some uncertainty. It is currently the custom of many urologists, including the authors, to accept as final the clinical diagnosis of cancer based on the history and the rectal, cystoscopic and cystographic findings without pathological substantiation. In general this is a satisfactory basis on which to plan treatment. In older men the possibility of mistaken diagnosis, unlikely as it is, does not constitute a contraindication to this practice. The present series of cases includes 3 or 4 men in the fifth and sixth decades whose prostates regressed to such a degree that they no longer were recognizable as carcinoma and whose obstructive symptoms had entirely disappeared. The possibility that the primary lesion may have been inflammatory rather than malignant and that the patient is being needlessly condemned to a life-time of estrogenic therapy and desexualization is not to be considered lightly. On the contrary, however, such favorable response to estrogenic therapy is frequently considered to confirm, rather than confuse the diagnosis.

The authors have made preliminary biopsy studies in few instances, in which radical prostatectomy was not considered. It is suggested that biopsy should perhaps be more frequently employed. The need of a simple but accurate biopsy method is emphasized. The authors are undertaking a critical analysis of various aspiration and punch type biopsy techniques for which they have thus far had little enthusiasm. The established perineal biopsy could well be more frequently employed even in cases in which there is no thought of total prostatectomy. It is recognized by the authors that total extirpation of cancer, when possible, is the only certain cure of the disease. In the small group without evidence of extracapsular invasion or other contraindication, radical prostatectomy is advocated, and 6 cases so treated were included in this series. Of 4 cases in which operation was performed elsewhere, 2 suffered local recurrence and 2 were too recent to follow. Two such cases have been operated upon by the authors; good results have been achieved in both thus far.

SUMMARY

Complete or virtually complete bladder neck obstruction due to cancer of the prostate was relieved by catheter drainage and estrogenic therapy in 16 (75 per cent) of 20 patients studied.

Surgical treatment was eventually necessary in only 6 (8 per cent) of 75 cases of cancer of the prostate selected without regard to the degree of obstruction and treated primarily with estrogens alone.

The period of observation varied from one to five years.

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MALIGNANT DISEASE OF THE TESTICLE

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It is the scope of this paper to discuss the diagnostic difficulties encountered in 32 patients admitted to Walter Reed General Hospital because of malignant diseases of the testicles during the 3½ year period ending December 31, 1949. Although tumors of the testis are rare, they occur with sufficient frequency and early diagnosis is of such great importance that every physical examination should include a careful evaluation of the scrotal contents. These tumors occur most frequently in the ages 20–40 years. Because of this age factor a high incidence is noted in recruits during a general mobilization. Before the mobilization in 1940, a series of more than 50 testicular tumors was rarely reported. In a short time after mobilization, Lowry, et al. reported 100 cases at the Lawson General Hospital, Lewis reported 250 at Walter Reed General Hospital, and Friedman and Moore reported 922 at the Army Institute of Pathology.

ETIOLOGY

Nothing more is known of the active etiologic factors than is known of the cause of the malignant tumors in general. Trauma as an etiologic factor is uncertain since the trauma in almost all the cases was merely accidental and did not influence the origin of the disease. Trauma was noted in 20 per cent of the cases reported by Gordon-Taylor and Till. The incidence in undescended testes has been estimated to be 20 to 40 times as great as in normally placed organs.

The clinical types usually seen are 1) tumors with slow, insidious, painless, but relentless onset; 2) the "hurricane" type with an incredibly rapid onset; 3) tumors of slow growth, as in No. 1, but with sudden increase in size; and 4) the unobtrusive type first recognized by metastases. In considering the differential diagnosis it is important to keep these types in mind.

The structural patterns as classified by Friedman and Moore are 1) seminoma, 2) embryonal carcinoma, 3) teratocarcinoma, 4) teratoma, and 5) miscellaneous. This simplified classification gives the clinician a better working basis than the more elaborate nomenclature.

Early diagnosis followed by the proper treatment is the most important factor in the prognosis of tumor of the testis. The differential diagnosis is not difficult. Every mass in the scrotum should be considered malignant until proved to be otherwise. Bimanual examination is imperative. In the case of painful lesions, not often found in malignancy, general anesthesia may be necessary in order that the condition of the scrotal contents may be properly evaluated. Epididymitis, thick-walled hydroceles, and hematoceles are the most difficult to differentiate. Hydroceles that have been tapped frequently are

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Read at the annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 10, 1950.

very confusing. Careful estimation of the size, contour, and weight of the testis should be made. A malignant tumor of the testis feels heavier than other masses on bimanual palpation. The clinical recognition is a matter of exclusion. Early diagnosis is life saving. The Aschheim-Zondek hormone test offers little in establishing an early diagnosis, and may even be confusing because the usually negative response may give a sense of false security and cause loss of valuable time in beginning proper treatment. It is important that the diagnosis be established and treatment be initiated before metastases take place. In Lewis' series, metastatic lesions were present in 43 per cent on admission to the hospital and metastases developed in 28 per cent soon after admission, a total of 71 per cent metastases, caused by delay in diagnosis and treatment.

TREATMENT

Orchiectomy and resection of the spermatic vessels and the iliac and retroperitoneal lymph glands to the renal pedicle has been the treatment for all cases. Postoperative x-ray treatment has been carried out in case of tumors sensitive to radiation therapy.

ANALYSIS OF CASES

In the 3½ years ending December 31, 1949, thirty-two patients were admitted to Walter Reed General Hospital who had malignancy of the testis. The patients ranged from 18 to 43 years of age, the average being 26 years. The initial symptom in all cases except one was painless swelling of the testis. In only 1 case was pain described by the patient at the onset and he did not seek medical attention for 9 months. In several others intermittent, vague, dull pain was noted later, at times associated with moderate pains in the lower abdomen. This is of interest since 9 of the patients were treated for epididymitis because of pain and tenderness in the testis, although they all described painless swelling that antedated the pain.

On physical examination the testis was enlarged and firm in 25 of the cases. In only 7 were nodules described. This was probably caused by failure of the examiner to palpate the testis carefully. The initial diagnosis in 18 cases (56 per cent) was tumor. In the other 14 the diagnoses were: epididymitis, 9; hydrocele, 2; varicocele, 1; and no diagnosis, 2. The last 2 patients, were, however, treated for epididymitis. The interval from the onset of symptoms until medical advice was sought was from 1 day to 2 years. The average interval was 3.5 months, but 37 per cent of the patients sought attention within 2 weeks. One patient with symptoms for 7 years is disregarded. Of the patients with metastases the interval was from 1 day to 11 months. The average interval was 4.2 months. Thirty per cent of the patients sought attention within 2 weeks. In the patients in whom the original diagnosis was erroneous, the interval from the onset of symptoms until a correct diagnosis was from 3 days to 4 years (average 4.6 months). The interval from the date of diagnosis of tumor until operation was 1 to 60 days (average 10). In only 7 patients was this over 25 days. This indicates that these patients should be treated as emergencies and given definitive treatment as soon as possible.

The pathologic diagnoses following operation are shown in table 1. Fourteen patients, or 44 per cent, had metastases, at the time of retroperitoneal gland dissection. No metastases were found to develop following this surgical procedure, however, this series is too small and too recent for proper evaluation of that factor. Nine, or 28 per cent of the patients, died and all of these had metastases at the time of operation. The hormone test was performed on 27 patients and was positive in 3. Two of these had choriocarcinoma and one teratocarcinoma. This indicates that history and physical examination are paramount and that treatment should not await the results of the hormone test. The transfer of one patient to another hospital was delayed 3 weeks awaiting the report from a regional laboratory, and when reported the test was negative. There was a history of trauma in 4 patients, but this was either vague or the injury had occurred some years prior to the onset of symptoms.

TABLE 1. *Pathologic diagnoses and metastatic involvement in 32 patients with testicular tumor*

	TUMOR	METASTASES PRESENT
Seminoma	10	2
Teratocarcinoma	8	3
Embryonal carcinoma	7	4
Choriocarcinoma	4	4
Chorio-epithelioma	1	0
Sarcoma, epididymis	1	1
Carcinoma, epididymis	1	0
Total	32	14

REPORT OF CASES

Case 1. A 22 year old man was admitted to an overseas hospital June 7, 1946 complaining of painless swelling and firmness of the left testis of 5 months' duration. This had increased rapidly in size in the 3 months preceding admission. Two weeks prior to admission he had been hospitalized for hepatitis and had undergone a physical examination in which no testicular abnormality had been noted. Examination on admission revealed the left testis to be twice the normal size, smooth and hard in consistency. On June 8 a simple orchiectomy was performed. The hormone test was negative. He was transferred to Walter Reed General Hospital and on August 1 a retroperitoneal gland dissection was performed. The pathologic diagnosis was teratocarcinoma, and no metastases were found. He received postoperative radiation.

Case 2. A 22 year old man first noted painless swelling of the left testis on October 13, 1948. On December 24 he noted a gnawing suprapubic pain. He was admitted to an overseas station hospital with a diagnosis of epididymitis, treated with penicillin and heat, and discharged as cured. Because of continued swelling he was readmitted January 25, 1949 and transferred to a general hospital, where an orchiectomy was performed. The hormone test was positive. He was transferred to Walter Reed General Hospital and on February 8 a radical retroperitoneal gland dissection was performed. Postoperative radiation therapy was given. The pathologic examination showed choriocarcinoma, probably chorio-epithelioma, with lymphatic and vascular extension. He died of metastases June 18, 1949.

Case 3. A 19 year old man noted a firm, nontender enlargement of the right testis early in March 1947. About the end of March he was admitted to an overseas hospital where he was treated for 3 weeks with penicillin and ice bags. The scrotum was tapped but no fluid was obtained. He was discharged to duty and returned to the United States for separation. While on terminal leave he reported to an Army hospital where a diagnosis of tumor, hydrocele and organized hematoma was considered. After 6 weeks he was transferred to Walter Reed General Hospital where he was admitted on June 27. A radical orchiectomy performed on July 1 revealed retroperitoneal metastases, which necessitated a right nephrectomy. After a course of postoperative radiation he was discharged January 24, 1948. On November 2 he was readmitted with chest pain, hemoptysis and weakness of 1 month's duration. He died on November 26 with multiple pulmonary metastases.

SUMMARY

In a series of 32 cases of tumor of the testis, the initial diagnosis of tumor was made in 18. Fourteen patients had metastases on admission. The average time interval from onset to medical attention was 3.8 months. The average time from first medical attention to definitive treatment was 2 months. The average interval from tumor diagnosis to treatment was 10 days. In those patients in whom the initial diagnosis was incorrect an average of 4.6 months elapsed before proper treatment was instituted. The hormone test was rarely a useful factor in making a proper diagnosis. The results of this test were often confusing and even caused delay in beginning the treatment. Early diagnosis and immediate treatment will greatly reduce the mortality in malignancy of the testis. All scrotal masses should be considered malignant until proved otherwise by adequate examination or operation.

REFERENCES

Friedman, N. B. and Moore, R. A.: Tumors of the testis: Report on nine hundred twenty-two cases. Military Surg., 99: 573, 1946.

Gordon-Taylor, C. and Till, A. S.: Malignant disease of testicle with special references to neoplasm of undescended organ. *Brit. J. Urol.*, **10**: 1–45, 1938.

Lewis, L. G.: Testis tumors: Report on 250 cases. J. Urol., 59: 763, 1948.

Lowry, E. C., Beard, D. E., Hewit, L. W. and Barner, J. L.: Tumor of the testicle: Analysis of one hundred cases: A preliminary report. J. Urol., 55: 373, 1946.

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SOURCES OF DANGER IN URINARY EXTRAVASATION: THE HAZARD OF PERFORATION DURING TRANSURETHRAL PROSTATECTOMY

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From the Department of Surgery, Division of Urology, Stanford University School of Medicine, the University of California School of Medicine and the Veterans Administration Hospital, San Francisco, Calif.

Twenty-five years ago the mortality rate resulting from urinary extravasation was 50 per cent and the accepted form of treatment was wide drainage and suprapubic cystostomy as soon as the diagnosis was established. In recent years the number of mortalities has been reduced and more conservative forms of treatment are being introduced. The subject is of special interest at the present because the threat of urinary extravasation is increased by the trend towards more radical transurethral prostatectomy.

Several factors make estimation of the actual frequency of this complication during transurethral operation difficult: many perforations are not recognized clinically; others, although recognized, are not noted on the hospital chart; and of those that receive attention, few are reported in the literature.

As a basis for formulating principles of treatment in perforation during transurethral resection, we have evaluated the sources of danger by studying a series of cases in which extravasation occurred. These cases provided general information and pointed to some possible etiologic factors, but were not suitable for critical analysis. Laboratory data were insufficient and the numerous variables prohibited conclusions. It was therefore necessary to evaluate the factors observed experimentally in order to develop a rational plan of treatment. The discussion that follows, then, is presented in three parts: 1) study of the sources of danger in cases of urinary extravasation, 2) description of an experimental study of the factors observed and 3) recommendations for the treatment of urinary extravasation following transurethral prostatectomy.

CLINICAL STUDY

Thirty-six consecutive cases of extraperitoneal extravasation encountered during the years from 1930 to 1940 were chosen from hospital files. Cases from this period, before the widespread use of the effective antibacterial drugs, were studied in order to assess the influence of infection. By including only cases of extraperitoneal extravasation from the male urethra distal to the urogenital diaphragm, the extent of extravasation could be evaluated as a factor.

Extravasation was caused by peri-urethral abscess in 3 cases, by rupture of the urethra in 7 and by stricture of the urethra in 26.

Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 18, 1950.

Sponsored by the Veterans' Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans' Administration.

Supported in part by the Christine Breon Fund for Medical Research, University of California School of Medicine.

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Treatment in all 36 cases consisted of incision and drainage and suprapubic diversion of urine. The mortality rate was 36 per cent.

The duration of extravasation before treatment in the 33 cases in which it was known ranged from less than 1 day to 14 days and did not seem to influence the outcome (table 1).

The extent of extravasation had a decided effect on the mortality rate (table 2); the more extensive the extravasation, the greater the number of deaths. No fatalities followed extravasation into either the penis or the perineum alone, but extension into the scrotum and into the anterior abdominal wall was accompanied by a progressive rise in the mortality rate.

TABLE 1. *Duration of extravasation prior to treatment. No correlation with mortality*

DURATION, DAYS	CASES		
	Total	Recovery	Death
Less than 1	6	3	3
2 to 4	6	4	2
5 to 7	13	11	2
8 to 10	3	2	1
10 to 14	5	2	3
Not known	3	1	2
Totals	36	23	13

TABLE 2. *Extent of extravasation. The more extensive the extravasation, the higher the mortality rate*

SITES	CASES			MORTALITY RATE
	Total	Recovery	Death	
Penis	1	1	0	0
Perineum	5	5	0	0
Perineum and external genitalia	19	15	4	21
Perineum, external genitalia and abdominal wall	11	2	9	82
Totals	36	23	13	36

Bacteriologic studies had been recorded in 29 cases (table 3). Death occurred only in the presence of infection (in 11 of 25 cases). Eleven patients had either a coccal or a bacillary infection; 14 had a mixed infection and 4 had none.

In 17 cases the concentration of nonprotein nitrogen had been determined (fig. 1). The findings are of particular interest because recovery occurred in 4 of the 12 patients with high levels and in 3 of these 4 cases the levels exceeded those in the group that died.

Necropsy had been carried out in all 13 cases. At the site of extravasation there were all gradations of an inflammatory process: acute cellulitis, abscess formation with vascular thrombosis, and gangrene. As noted by Bailey and Huddy, infection and suppuration were no respecters of anatomical barriers and extravasation was not always limited to the fascial planes so precisely described in textbooks. In all the cases, toxemic changes of the viscera were evident. On microscopic examination of the heart, liver and kidneys, there were intercellular extravasations of blood and cloudy swelling (fig. 2). Additional findings were bronchopneumonia in 6, pyelonephritis in 3, peritonitis in 1 and multiple fractures of the pelvis in 3.

TABLE 3 *Incidence of infection. No deaths in the absence of infection*

INFECTING ORGANISMS	CASES			MORTALITY RATE
	Total	Recovery	Death	
None.	4*	4	0	0
Bacillus proteus	1	2	0	44
Staphylococci and streptococci	2	1	1	
Bacillus coli	7	4	3	
B coli, staphylococci and streptococci	13	7	6	
Clostridium welchii, staphylococci and streptococci.	1	0	1	
Not known	7	5	2	28.5
Totals	36	23	13	36.1

* Duration prior to treatment · 2 hours, 3, 3, and 7 days, respectively

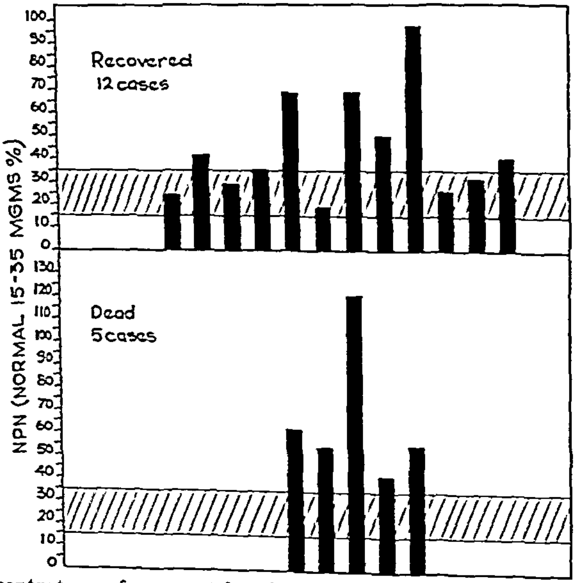

FIG. 1 Concentration of nonprotein nitrogen at height of reaction in 17 cases. No correlation with mortality rate.

One feature especially attracted our attention: some of the patients succumbed several days after the extravasation had been relieved by wide incision and drainage and diversion of urine when they were apparently improving. Decline in temperature and fall of the leukocyte count indicated that the infection was subsiding. There were, however, certain untoward signs: the pulse rate rose gradually, the heart sounds became distant, cardiac murmurs sometimes developed and in most of the cases the blood pressure dropped (fig. 3).

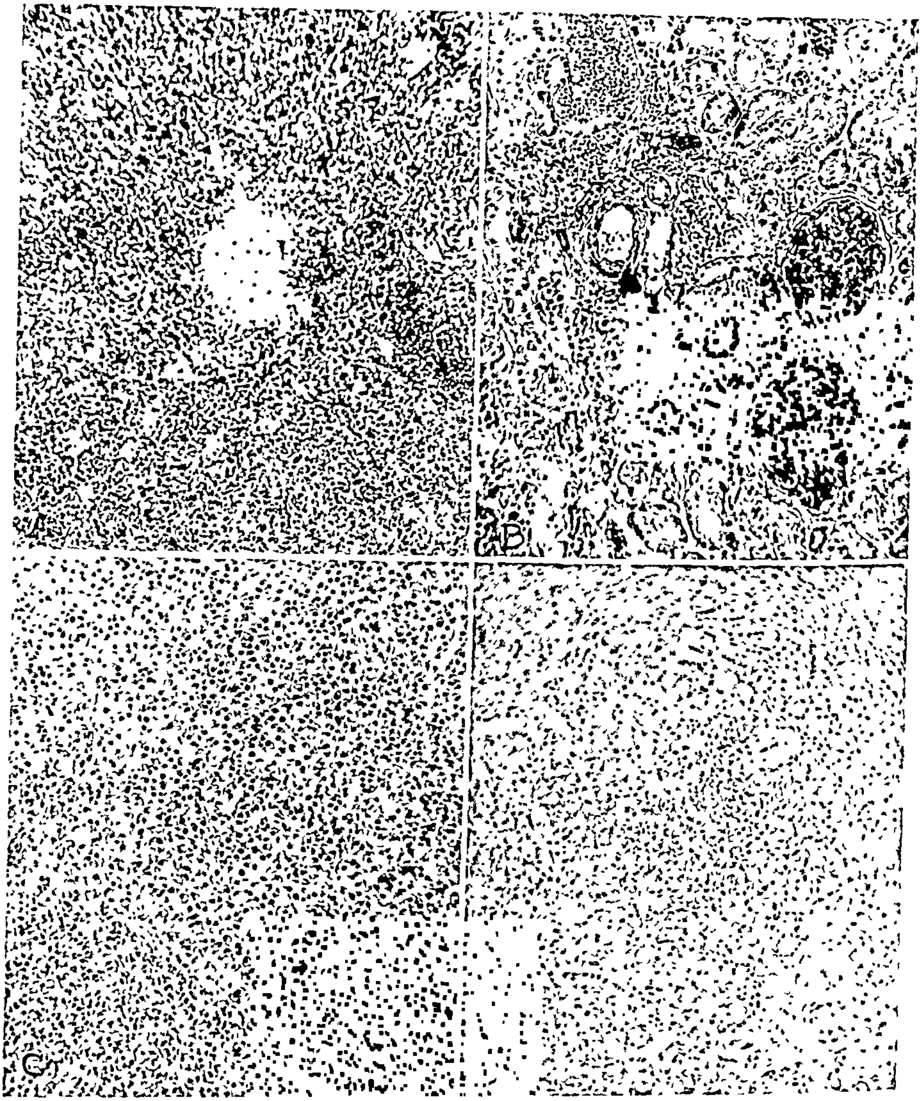

FIG. 2. Photomicrographs of tissues of patients who died as result of urinary extravasation. *A*, spleen; interstitial hemorrhage. *B*, kidney; interstitial hemorrhage, myelocytic infiltration and granular degeneration of tubules. *C*, adrenal; focal degeneration. *D*, liver; interstitial hemorrhage, cloudy swelling and fatty degeneration. Compare with figure 4.

These seemed to be signs of myocarditis. The question therefore arises: Is it possible that a toxin generated by the inflammatory process in urinary extravasation had produced toxic myocarditis similar to that which may complicate diphtheria? Numerous electrocardiograms had been made in these cases, but the results were inconclusive. Most of the patients were elderly and at necropsy the arteriosclerotic changes in the heart were indistinguishable from myocarditic changes.

In these 36 cases, contrary to common belief, the factors of nitrogen retention and the duration of extravasation prior to treatment exerted no pronounced deleterious influence. Infection and extensive extravasation, however, provided a serious hazard and deaths were more numerous in the cases in which these were present. With the general information gained from these cases, experimental studies were planned in an attempt to determine which among the factors are responsible for the complications of urinary extravasation.

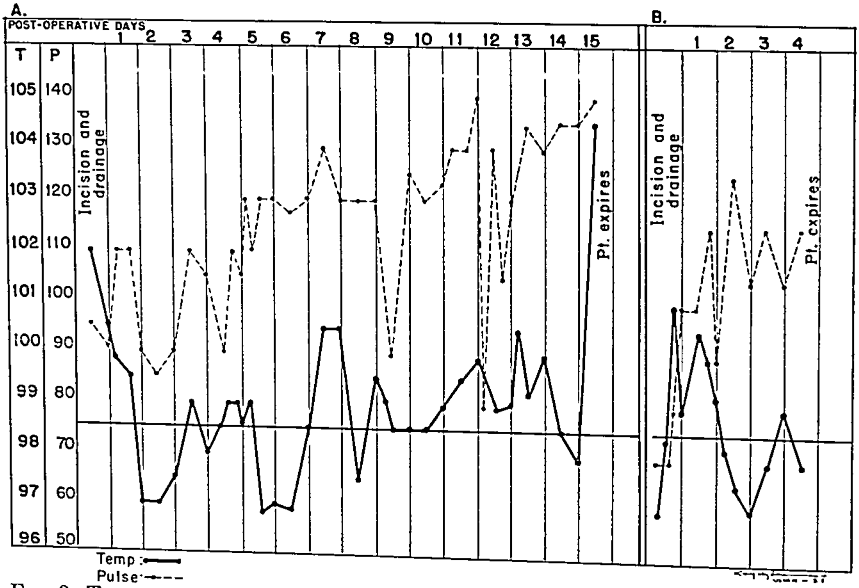

FIG. 3. Two cases illustrative of those suggesting toxic myocarditis. Case A, note gradual rise in pulse rate from 90 to 140 in a period of 15 days without coincident rise in temperature. Case B, death 4 days after drainage; rise in pulse rate while temperature fell to normal.

EXPERIMENTAL STUDIES

In all of the following experiments in which solutions were given to experimental animals, the injections were made subcutaneously into the thigh in order to simulate the conditions of extravasation.

The results were indicated as follows (fig. 4):

No reaction: No local or generalized observable change.

Mild reaction: Slight induration disappearing in 4 to 6 days, no rise in temperature.

Severe reaction: Extensive swelling and induration at the site of injection, sometimes followed by gangrene and ulceration (fig. 5), elevation of rectal temperature to 38 to 40C, diffuse cellulitis with abscess formation.

Died: Death occurred within a few minutes to 6 days, changes observed in a severe reaction, evidence of toxicity at autopsy, cloudy swelling of the heart, liver and kidneys and congestion of the spleen (fig. 6).

Experiment 1. Effects of bacteria (table 4, fig. 7). Seven different solutions were selected which either might be present in areas of extravasation or are favorable for bacterial growth. Fifty-six dogs, weighing about 12 kg. each, were used. Bacteria, all of which had been *encountered in the clinical series,* were cultured in broth for 24 hours and the concentration at the time of injection was about 1 billion per milliliter.

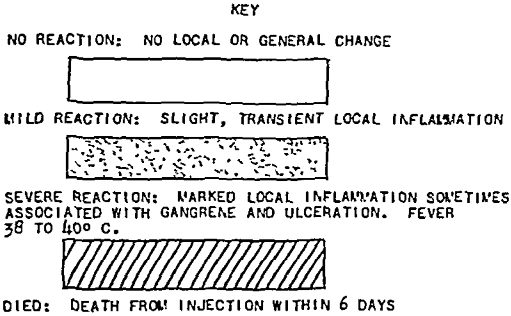
KEY
NO REACTION: NO LOCAL OR GENERAL CHANGE
MILD REACTION: SLIGHT, TRANSIENT LOCAL INFLAMMATION
SEVERE REACTION: MARKED LOCAL INFLAMMATION SOMETIMES ASSOCIATED WITH GANGRENE AND ULCERATION. FEVER 38 TO 40° C.
DIED: DEATH FROM INJECTION WITHIN 6 DAYS

FIG. 4. In charts that follow (figs. 7, 9, and 12) reactions are represented according to above key.

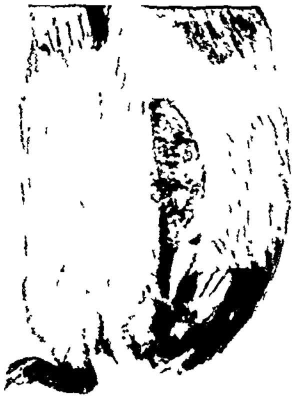

FIG. 5. Severe reaction in guinea pig. Gangrene and ulceration 1 week after injection of 4.5 cc human urine with 0.5 cc B. coli culture. Although injection was made into thigh, inflammatory process extended far up abdomen and down into leg causing contracture of that extremity.

The solutions alone did not invoke any tissue reaction, but the solution plus bacteria usually caused a severe reaction or even death. Human urine evidently provided better conditions for bacterial growth than the other substances because the only deaths occurred in dogs that had received urine containing bacteria. Bacillus coli (Escherichia coli) gave rise *to a high percentage of the severe reactions. An effort was made to determine whether myocarditis had caused the deaths, but the few electrocardiographic irregularities were far* from conclusive.

Experiment 2. Concentration of bacteria (table 5). Cultures of the same strain of B. coli were mixed with either saline, human urine or heart-brain infusion of broth immediately before injection so that the bacterial concentrations of the mixtures injected varied. In the control group, sterile solutions were injected.

As was expected, no reaction followed injection of the sterile solutions, and the animals all died when high concentrations were given. Again, urine was favorable for bacterial growth, markedly superior to sterile saline or saline containing bacteria. The results in the group that received saline can be considered to represent those of bacteria alone, uninfluenced by the medium. The reaction, then, reflected the number of bacteria and the medium in which they were injected (fig. 8).

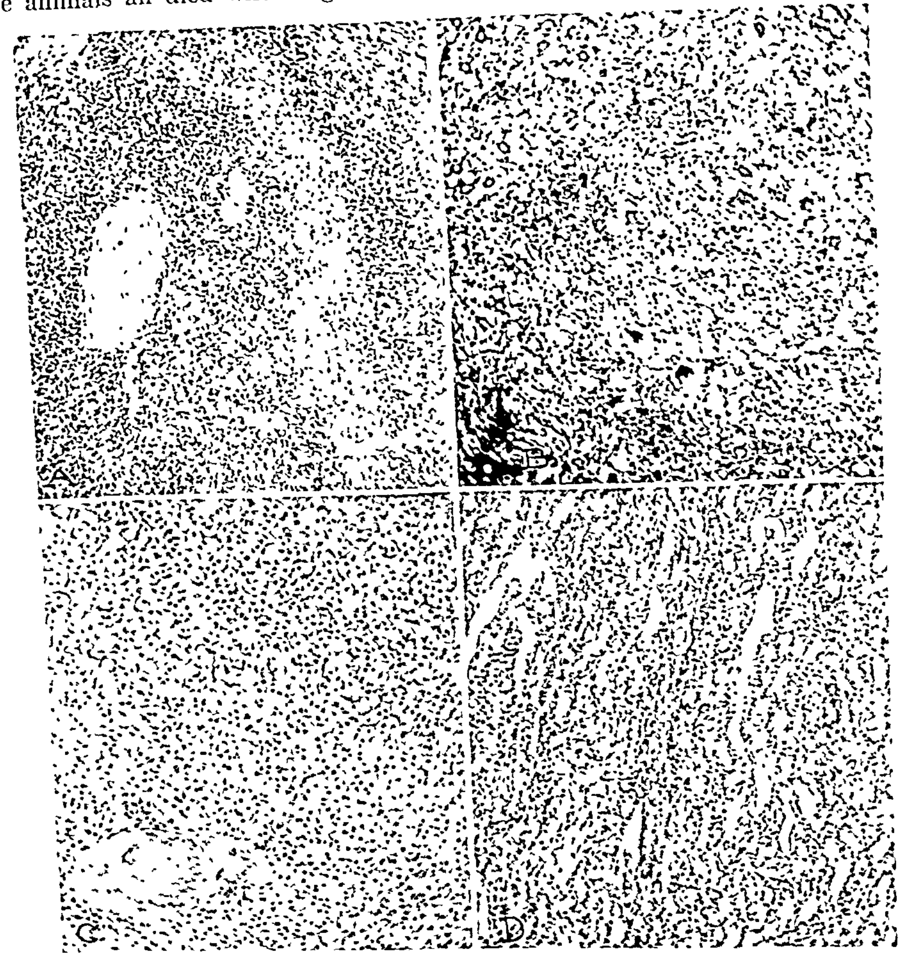

Fig. 6. Photomicrographs of tissues of guinea pigs that died as result of subcutaneous injection of B. proteus-urine culture. *A*, spleen; extravasation of erythrocytes into parenchyma. *B*, kidney; interstitial hemorrhage and myelocytic infiltration. *C*, liver; cloudy swelling and interstitial hemorrhage. *D*, lung; congestion and cloudy swelling; compare with figure 6.

Experiment 3. Type of bacteria (table 6). This experiment was planned to study the reaction caused by 4 different bacteria encountered in the clinical study

TABLE 4 *Effect of bacteria and different media*

PREPARATION INJECTED	NO OF DOGS	NO REACTION		MILD REACTION		SEVERE REACTION		DIED	
		No	%	No	%	No	%	No	%
Human urine—20 cc	8	8	100						
" 9 cc Hem strep. 1 cc	2					2	100		
" 9 cc B coli 1 cc	11			2	18	4	36	5	45
" 9 cc Staph. aureus 1 cc	2							2	100
Normal saline—20	3	3	100						
" 9 cc Hem. strep 1 cc	1	1	100						
" 9 cc B coli 1 cc	3					3	100		
" 9 cc Staph aureus 1 cc	1					1	100		
Synthetic urine (Bodansky's) 20 cc	2	2	100						
" 9 cc B coli 1 cc	3					3	100		
Dog's blood—20 cc	1	1	100						
" 9 cc Hem strep 1 cc	1	1	100						
" 9 cc Staph aureus 1 cc	1			1	100				
" 9 cc B coli 1 cc	2					2	100		
Glucose (10% sol)—20 cc	2	2	100						
" 9 cc B coli 1 cc	2					2	100		
Broth—20 cc	3	3	100						
" 9 cc B coli 1 cc	3					3	100		
Urea (2% sol)—20 cc	2	2	100						
" 9 cc B coli 1 cc	3					3	100		

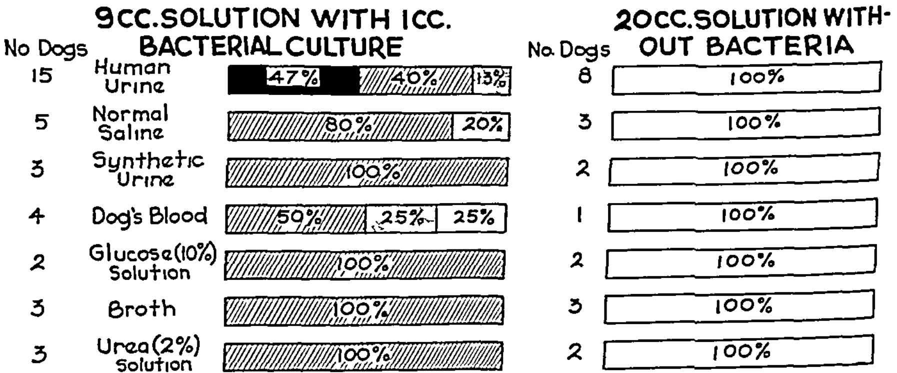

FIG 7 Effect of bacteria and of various culture media Solutions alone were largely innocuous, but when cultures were added, severe inflammatory reactions or death ensued Note efficacy of urine as culture medium

when they were combined with urine before injection. Fifty guinea pigs were used. B. coli was the most lethal, and some of the animals that received B. proteus (Proteus vulgaris) died, but none of the animals that received hemolytic streptococci or Staphylococcus aureus died.

TABLE 5. *Effect of concentration of bacteria. Direct correlation with mortality rate*

PREPARATION INJECTED	NO OF GUINEA PIGS	NO REACTION		MILD REACTION		SEVERE REACTION		DIED	
		No	%	No	%	No	%	No	%
Saline—10 cc	10	10	100						
" 4.875 cc B coli 0.125 cc	20			12	60	5	25	3	15
" 4.75 cc " 0.25 cc	20			14	70	2	10	4	20
" 4.5 cc " 0 5 cc	20			12	60	3	15	5	25
" 4.5 cc " 1.0 cc	20							20	100
Human urine—10 cc	40	40	100						
Urine 4.875 cc B. coli 0.125 cc	30			5	17	16	53	9	30
" 4.75 cc " 0.25 cc	20					6	30	14	70
" 4.5 cc " 0.5 cc	20					9	45	11	55
" 4 0 cc " 1.0 cc	20							20	100
Broth—10 cc	10	10	100						
" 4.875 cc B. coli 0.125 cc	10					3	30	7	70
" 4 75 cc " 0.25 cc	10					2	20	8	80
" 4 5 cc " 0.5 cc	10					1	10	9	90
" 4 0 cc " 1.0 cc	20							20	100

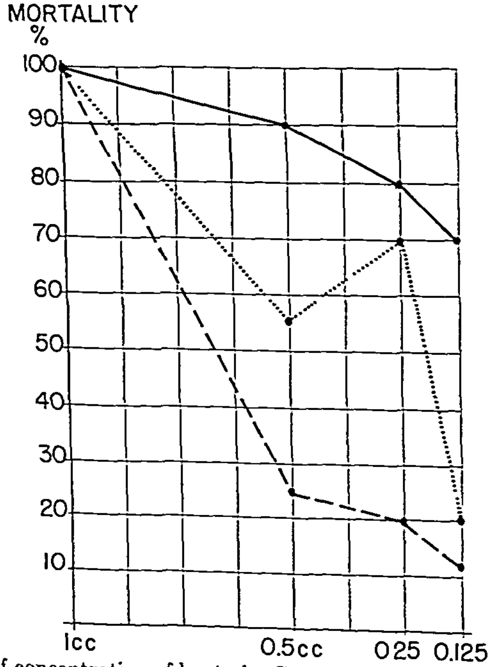

FIG 8 Effect of concentration of bacteria. Graph also reflects that urine is good culture medium Culture contained about 1 billion B. coli per cubic centimeter; 280 guinea pigs were used

Broth ————————————

Human Urine

Normal Saline - - - - - - - - - -

TABLE 4 *Effect of bacteria and different media*

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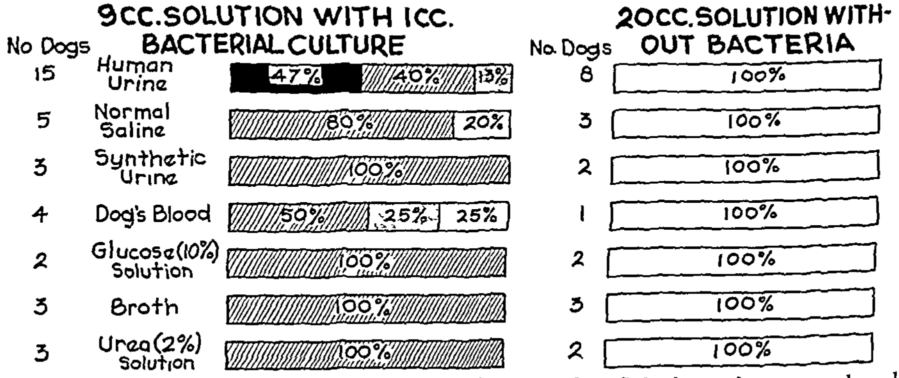

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when they were combined with urine before injection. Fifty guinea pigs were used. B. coli was the most lethal, and some of the animals that received B. proteus (Proteus vulgaris) died, but *none of the animals that received hemolytic* streptococci or Staphylococcus aureus died.

TABLE 5. *Effect of concentration of bacteria. Direct correlation with mortality rate*

PREPARATION INJECTED	NO. OF GUINEA PIGS	NO REACTION		MILD REACTION		SEVERE REACTION		DIED	
		No	%	No	%	No	%	No	%
Saline—10 cc	10	10	100						
" 4.875 cc B. coli 0.125 cc	20			12	60	5	25	3	15
" 4.75 cc " 0.25 cc	20			14	70	2	10	4	20
" 4.5 cc " 0.5 cc	20			12	60	3	15	5	25
" 4.5 cc " 1.0 cc	20							20	100
Human urine—10 cc	40	40	100						
Urine 4.875 cc B. coli 0.125 cc	30			5	17	16	53	9	30
" 4.75 cc " 0.25 cc	20					6	30	14	70
" 4.5 cc " 0.5 cc	20					9	45	11	55
" 4.0 cc " 1.0 cc	20							20	100
Broth—10 cc	10	10	100						
" 4.875 cc B. coli 0.125 cc	10					3	30	7	70
" 4.75 cc " 0.25 cc	10					2	20	8	80
" 4.5 cc " 0.5 cc	10					1	10	9	90
" 4.0 cc " 1.0 cc	20							20	100

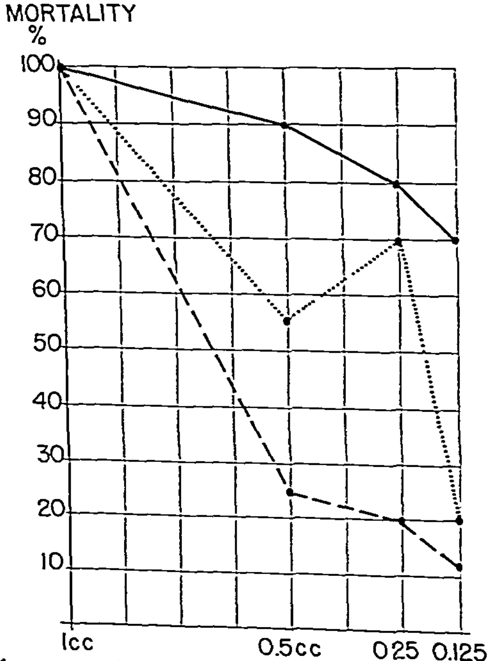

FIG. 8. Effect of concentration of bacteria. Graph also reflects that urine is good culture medium. Culture contained about 1 billion B. coli per cubic centimeter; 280 guinea pigs were used.

Broth ————————

Human Urine

Normal Saline - - - - - - - - - -

*Experiment 4. Toxicity.** (*table 7, fig. 9*). In an effort to determine whether death resulted from toxicity, 50 guinea pigs were given bacterial cultures in urine and another 50 were given bacteria-free filtrates of the culture-urine mixture.

One loopful of a culture of bacteria was inoculated into each of three test tubes containing 10 cc broth and the tubes were placed in an incubator at 37C for 24 hours. For the toxin experiment, the contents of the 3 tubes were added to 250 cc of sterile human urine and incubated at 37C for 24 hours. As an additional test to compare urine and saline, the contents of 3 tubes containing B. proteus cultures were added to 250 cc of sterile saline and incubated in the same way.

TABLE 6. *Effect of different types of organisms. Higher mortality rate with Bacillus coli and B. proteus*

ORGANISM*	GUINEA PIGS		MORTALITY RATE
	Total	Deaths	
Bacillus proteus	17	5	29
Bacillus coli	18	11	61
Hemolytic streptococci	6	0	0
Staphylococcus aureus	9	0	0

* 1 cc of culture (approx. 1 billion organisms) and 4 cc of urine.

TABLE 7. *Comparison of toxicity of cultures and bacteria-free filtrates*

PREPARATIONS USED	NO OF PIGS	NO REACTION		MILD REACTION		SEVERE REACTION		DIED	
		No.	%	No	%	No	%	No.	%
Proteus-urine culture	17	5	29			7	41	5*	29
Proteus-urine filtrate	17	15	88					2*	12
Proteus-saline culture (control)	13			13	100				
Proteus-saline filtrate (control)	13	8	62	5	38				
Coli-urine culture	18			3	17	4	22	11†	61
Coli-urine filtrate	18	18	100						
Hemolytic. strep. urine culture	6					6	100		
Hemolytic-strep. urine filtrate	6	6	100						
Staph. aureus-urine culture	9					9	100		
Staph. aureus-urine filtrate	9	9	100						

* Death within 1 hour.
† Death within 3 days.

The broth-urine cultures were then divided. Half of the animals were given 5 cc of the culture. From the remainder of the culture, a bacteria-free filtrate was prepared with a Seitz filter and negative pressure of 30 to 50 mm. of mercury was applied. Filtrates were also prepared with the urine-free B. proteus culture in the same way. Stained smears and cultures proved the filtrates to be free of bacteria.

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* We are indebted to Dr. Campbell McCullough for his assistance with this experiment.

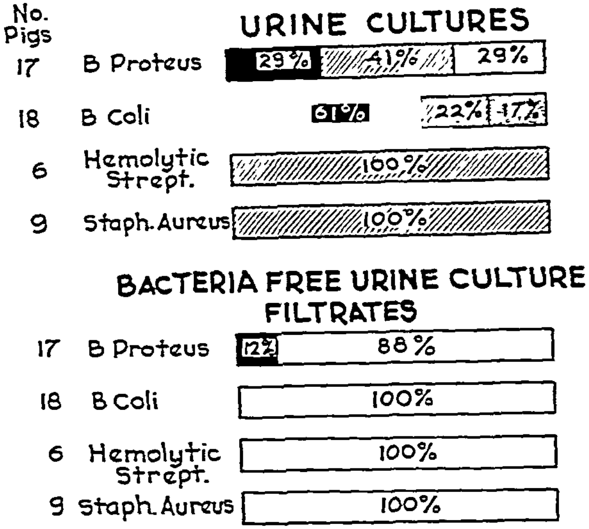

Fig. 9. Toxicity of cultures in comparison to bacteria-free filtrates of cultures containing urine. Again B. proteus and B. coli were more lethal. Note toxicity of B. proteus-fre filtrate. Guinea pigs weighing approximately 250 gm. were used. Saline controls are show in table 7.

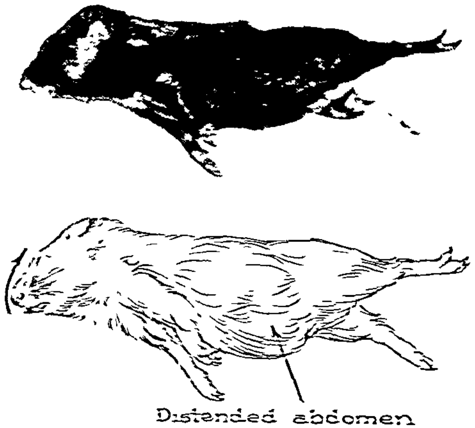

Fig. 10. Photograph and drawing of guinea pig that died in marked opisthotonos within half hour after injection of B. proteus and urine. Note abdominal distention. Animal also lost sphincter control. This death, characteristic of those caused by B. proteus, suggests that neurotoxin may have been present.

The results indicate that toxicity was a factor in the deaths due to B. proteus. These deaths occurred within 30 minutes of injection and were accompanied by unusual manifestations: The guinea pigs lost consciousness rapidly, became extended in the opisthotonus position (fig. 10) and had clonic contractions of the extremities. There were abdominal distention and fecal and urinary incontinence. The picture suggested that the agent was a neurotoxin. The deaths that followed injection of broth-urine cultures of B. coli occurred later, usually in about 3 days. These deaths may have been due to infection rather than toxin.

In general, except for the B. proteus group, the filtrates did not effect a reaction and the cultures invoked the usual high percentage of severe reactions or death. The reaction to saline cultures was again less marked than that to urine cultures.

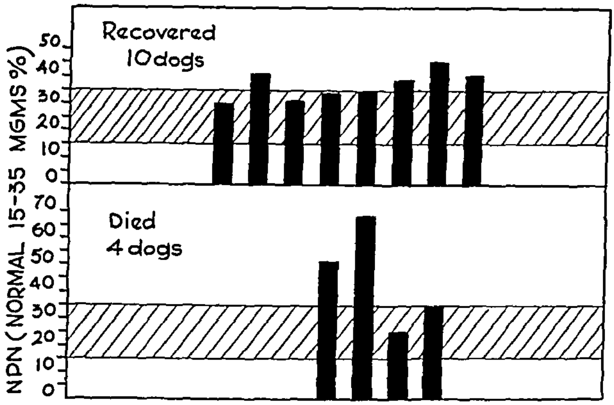

FIG. 11. Concentration of nonprotein nitrogen in 14 dogs from experiment 1 at height of reaction following injection of urine and bacteria. No correlation with mortality rate.

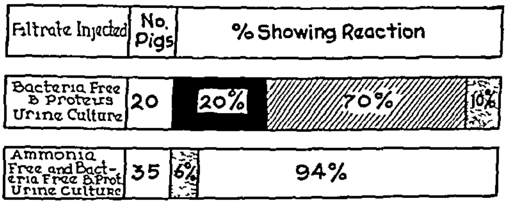

FIG 12. Difference in reaction between bacteria-free filtrates and deaminized bacteria-free filtrates of cultures containing urine and urea-splitting B. proteus. In presence of ammonium ion, deaths and severe reactions occurred; deaminized bacteria-free filtrates gave rise to few and only mild reactions.

Experiment 5. Nonprotein nitrogen (fig. 11). The concentration of nonprotein nitrogen was determined at the height of the severe reactions in 14 animals in experiment 1 that had received bacteria and urine. Although the highest levels were noted in the group that died, there is no direct correlation between the severity of the reaction and the degree of nitrogen retention.

Experiment 6. Ammonium ion (table 8, fig. 12) In determining the source of the toxic properties of the B. proteus filtrate, the effect of the NH_4 ion was tested by comparing the unmodified filtrate with a deaminized filtrate.

An infusion broth of motile B. proteus (urea-splitting) was cultured for 36 hours at 37C. Three tenths cubic centimeter of this infusion was added to 300 cc sterile human urine and cultured for 24 hours at 37C. The urine Proteus culture was filtered through a Seitz filter under negative pressure of 24 pounds and 5 cc bacteria-free filtrate was injected subcutaneously into the thighs of 20 guinea pigs. The remaining bacteria-free filtrate was liberated of its ammonia by bubbling ammonia-free air through it. Thirty-five guinea pigs were injected under conditions identical with those of the controls, using the same quantity of filtrate. Cultures were made of the filtrate to ascertain the absence of bacteria.

Of the 20 animals that received the unmodified B. proteus urine filtrate, 14 suffered from severe reactions and 4 died. Of the 35 animals that were given the deaminized bacteria-free filtrate, there were no severe reactions or deaths.

TABLE 8. *Effect of ammonia liberated by urea-splitting organisms*

MATERIAL INJECTED	GUINEA PIGS	REACTION			DEATHS
		None	*Mild*	*Severe*	
Bacteria-free filtrate from B. proteus-urine culture	20	0	2	14	4
Ammonia-free, bacteria-free filtrate from B. proteus-urine culture	35	33	2	0	0

TABLE 9. *Effect of ammonia preparations*

NUMBER OF GUINEA PIGS*	PREPARATION	AMOUNT	TRANSIENT TOXIC REACTION, RECOVERY	DEATH
1	Ammonium chloride	5 cc		+
1		1 cc		+
1	Ammonium oxalate	5 cc	+	
1		1 cc		+
1	Ammonium sulfate	5 cc		+
1		1 cc		+
1	Ammonium bromide	5 cc		+
1		1 cc		+
1	Ammonium carbonate	5 cc		+
1		1 cc	+	
1	Ammonia gas	5 cc	+	
1		1 cc	+	

* Weight: approx. 250 gm.

demonstrating the toxic properties of ammonia as derived from urea-splitting organisms in these experiments.

The well-recognized toxicity of ammonium compounds was borne out by this experiment.

In an additional 12 guinea pigs, subcutaneous injection of ammonium chloride, ammonium oxalate, ammonium sulfate, ammonium bromide and ammonia gas proved immediately toxic. The accompanying manifestations in 8 instances were typical of those from B. proteus. The remaining 4 animals became semicomatose for about 1 hour, but recovered without local signs at the site of injection (table 9).

The effect of urea-splitting organisms is to break down the urea of urine into ammonia and carbon dioxide: $NH_2CONH_2 \rightarrow NH_3$ and CO_2. This gives rise to a chemical reaction which is in itself damaging to tissues, although a violent toxic inflammatory reaction is superimposed by the presence of bacteria.

Experiment 7. pH. As nearly as could be determined, minor variations in the pH of the injected material did not affect its toxicity. In the experiments in which urine was used, the pH was 5 to 6.5 prior to the inoculation of bacteria. Although the addition of B. proteus converted the urine to an intensely alkaline solution with a pH of 12, it was established that the alkalinity was not the cause of the high incidence of toxic reactions in this group. Identical reactions were observed in animals receiving B. proteus-free urine filtrates in which the pH was brought to the neutral range by the addition of HCl. In a series of 20 guinea pigs, the injection of 20 cc of buffered sterile urine with a pH varying from 3 to 12 evoked no observable reaction.

Summary of experimental data. The experimental studies provide data to explain and augment the clinical observations. They afford proof that uninfected urine in amounts generally found in urinary extravasation is harmless, but that bacteria evoke a violently toxic inflammatory reaction. The severity of this reaction is directly proportional to the number and virulence of the infecting organisms, as well as to the efficacy of urine as a culture medium. Bacteria-free filtrates are much less toxic than bacterial cultures in urine, indicating that the toxin is probably an endotoxin closely allied to bacteria. An added toxic effect is imparted by the ammonium ion, such as is formed by urea-splitting organisms. The experimental findings are in accord with the clinical observations that the severity of the reaction bears no relationship to azotemia and that death is not caused by nitrogen retention. Death is apparently caused by toxins elaborated by bacteria in the presence of extravasated urine. Necropsy findings in the experimental animals are similar to those observed in the clinical cases and are compatible with a toxic process.

For the most part these experimental studies are in accord with those of previous investigators.

Yasuda and Sakabe, in an investigation of the toxicity of human urine, found that the average minimal lethal dose of intraperitoneally injected urine in healthy mice was 0.5 cc per gram of body weight. If this is applied to human beings, it would indicate that the absorption of 37,500 cc of urine would be necessary to cause death of a person weighing 75 kg.

Wolfer, in an experimental study of urinary extravasation, found that sterile urine causes reaction in the tissues only in enormous quantities, by virtue of mechanical irritation after long periods of constant infiltration, the reaction being caused by pressure. Similar changes were observed on injection of sterile water or normal saline solution. He also found that infected urine is very destructive to tissues, causing inflammation, necrosis and slough.

Bezza, in producing continued urinary extravasation by severing the ureter in rabbits, observed marked nitrogen retention, acidosis and an increase in the sodium chloride content of the blood. These changes were milder in limited extravasation.

CLINICAL MANAGEMENT

What, then, is the clinical significance of these findings, and how may they be applied to extravasation incident to transurethral resection? It would seem that these studies have brought out four considerations important in the formulation of principles of treatment:

1. Uninfected urine and common irrigating fluids are largely innocuous in one isolated extravasation.
2. The greatest hazard is from infection, the danger being directly proportional to the number of infecting organisms and their virulence.
3. The more continued and extensive the extravasation, the greater the risk when infection is present.
4. The better the cultural characteristics of the extravasated fluid, the greater the hazard; urine, glucose, urea, and glycine are more dangerous than water.

Here is provided a basis for revoking the antiquated dictum that drainage and diversion of the channel of urine must be employed immediately in all cases of extravasation. It is possible not only to say that such treatment is not indicated in all of these cases, but also to present rules for instituting open drainage.

For example, if extravasation is slight and there is no infection, satisfactory urethral catheter drainage eliminates the danger of continued leakage; there is no need for open drainage. No harm will result from the escape of small amounts of uninfected urine or irrigating fluid during operation. If, on the other hand, badly infected urine extravasates into the tissue planes, there is danger of a toxic inflammatory reaction, depending on the type, number and virulence of the infecting organism. Urea-splitting bacteria are especially dangerous. If a severe reaction is anticipated, open drainage is indicated without awaiting localizing signs in order to release as much of the toxic fluid as possible. Appropriate antibacterial therapy should be employed, of course, in all perforations and suspected perforations. It has been recommended that, because of the danger of injury in any resection, antibacterial therapy should always be employed preoperatively. When infection is minimal and extravasation is slight, it is justifiable to rely on antibacterial therapy and delay open operation, employing incision and drainage only if this becomes indicated by localizing signs.

The danger of the initial extravasation from perforation is minimized when water is employed and by the dilution of what bacteria are present by the copious lavage during operation. It is of extreme importance, however, to prevent continued extravasation. When relying on a urethral catheter for drainage following perforation, it is essential that drainage be unrestricted at all times and that no additional urine escape into the tissues. It has been shown how hazardous urine is in the presence of infection, and whenever a catheter is in place, infection is inevitable.

Because of the splinting effect of the muscles and fascial planes surrounding the prostate, surgical closure of an extraperitoneal perforation is usually not necessary. However, a perforation into the peritoneal cavity must always be sutured to avoid the danger of continued urinary leakage. We believe that in intraperitoneal perforations, suprapubic cystostomy is safer than ureth catheter drainage, once the opening is closed.

When open operation is indicated and the patient is in shock, it is well treat the shock preoperatively. A short delay will not affect the outcome concerns extravasation, and when patients are in shock they usually do n bleed excessively. What bleeding there is can usually be controlled temporari by the use of a bag catheter.

The diagnosis of perforation is usually made during resection. Fortunate this usually occurs near the end of the procedure. If it is found early the questi of whether to terminate the operation or to resect the remaining tissue aris If the perforation is small and there is no infection and localizing signs do n develop, one may proceed judiciously, being extremely cautious to avoid ove distention. If, on the other hand, the patient complains of pain, as is frequent the case even when spinal anethesia is used, operation should be terminated.

Usually the cystoscopic view and the evidence of fluid in the tissues indica the location and extent of the extravasation. When there is any doubt, especial about intraperitoneal leakage, there should be no hesitancy in taking a cyst urethrogram. Properly executed, this is the most reliable diagnostic method determining the location and extent of extravasation. It is important to fill t bladder and prostatic fossa to capacity and to make an emptying film aft evacuating all of the contrast medium. The use of cysto-urethrograms in perfor tion during transurethral operations is elaborated by Kenyon.

Diagnosis. The diagnosis of perforation, extravasation and infection may summarized as follows:

Perforation

Cystoscopic recognition of perforated capsule or bladder

Extravasation

Symptoms (may or may not be present)
  Pain in the operative area
  Abdominal pain
Signs (may or may not be present)
  Local: Suprapubic and rectal tenderness
    Suprapubic mass
    Bogginess on rectal examination
  General: Shock
Cysto-urethrography (most reliable diagnostic measure for determining th location and extent of extravasation)
  1. Plain x-ray
  2. Film with bladder and prostatic fossa filled to capacity. Use an innocuou contrast medium
  3. Emptying film

Infection

Preoperative findings of corroborative value
  Evidence of urinary infection
  Evidence of prostatic infection

Postoperative course
  Excessive febrile reaction
  Acute local signs

Treatment. The principles of treatment may be summarized as follows:

A. Antibacterial therapy should be employed following all perforations, near perforations or suspected perforations.

B. Urethral catheter drainage is indicated only in extraperitoneal extravasation and under the following circumstances:
   1. Apparent perforation without evidence of extravasation.
   2. Minimal extravasation, with or without infection.
   3. More extensive extravasation, without infection.

C. Incision and drainage and use of a urethral catheter is indicated only in extraperitoneal extravasation and under the following circumstances:
   1. Extensive extravasation with infection, particularly with urea-splitting bacteria.
   2. Delay in clinical improvement despite urethral catheter drainage usually in
      a. Large perforation with continued urinary leakage.
      b. Virulent infection in the area of extravasation.

D. Incision and drainage and suprapubic cystostomy are indicated in the following:
   1. All perforations into the peritoneal cavity (suture opening).
   2. Uncontrollable bleeding following perforation.
   3. Unsatisfactory urethral catheter drainage, usually because of continued bleeding from vessels at the site of perforation.

Illustrative cases. Four cases are presented to illustrate the application of these principles of treatment. All of the perforations occurred during transurethral resection. In addition to antibacterial therapy, the indicated forms of treatment were employed.

Case 1 (figs. 13 and 14): Patient P. B., white man. Age: 27 years. Prostatic median bar. Hemolytic staphylococcus urinary infection. Small extraperitoneal extravasation. *Urethral catheter drainage.*

The left lower aspect of the vesical neck was perforated after 2.5 gm. tissue had been removed. An emptying cysto-urethrogram at the time of operation showed a small extraperitoneal extravasation. Cysto-urethrograms on the first and second postoperative days showed no extravasation, although the temperature rose and there was suprapubic tenderness from the inflammatory process in the infected perforation. On the fifth day, fever recurred, but the absence of suprapubic or rectal tenderness indicated infection from some source other than additional extravasation. Fever subsided on further urethral catheter drainage.

Case 2 (fig. 15): Patient C. P., white man. Age: 71 years. Small trilobed benign prostatic hypertrophy. B. coli urinary infection. Slight extraperitoneal extravasation. *Urethral catheter drainage.*

The midlateral prostatic fossa was perforated near completion of resection, 19 gm. tissue having been removed. During the prolonged postoperative febrile course there was continued suprapubic and rectal tenderness from periprostatitis in the area of extravasation. In retrospect, it would seem that this patient would have done better with incision and drainage because of the duration of fever and local signs.

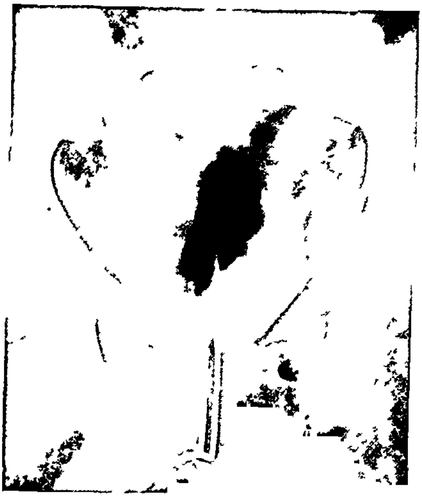

FIG 13 Case 1 Emptying cysto-urethrogram at time of operation. Note small extra peritoneal extravasation

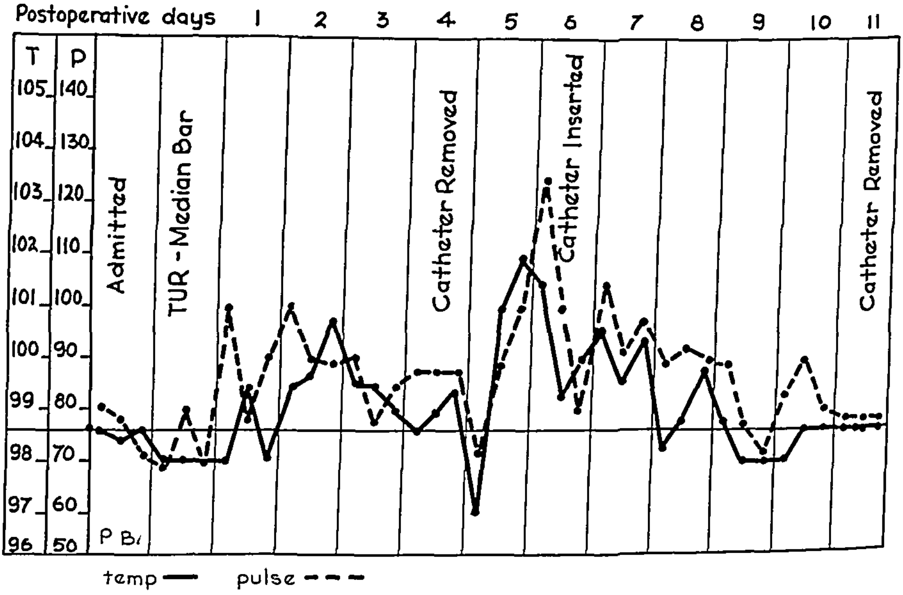

FIG. 14. Case 1 Hospital course

Case 3 (fig. 16): Patient J. P., white man. Age: 60 years. Small trilobed prosatic hypertrophy. No infection. Extraperitoneal extravasation: satisfactory rethral catheter drainage could not be established. *Suprapubic drainage and uture of perforation* followed by *urethral catheter drainage*. Uneventful course.

Perforation of anterior capsule occurred at its junction with the vesical neck fter removal of 13 gm. of tissue. The patient complained of suprapubic pain

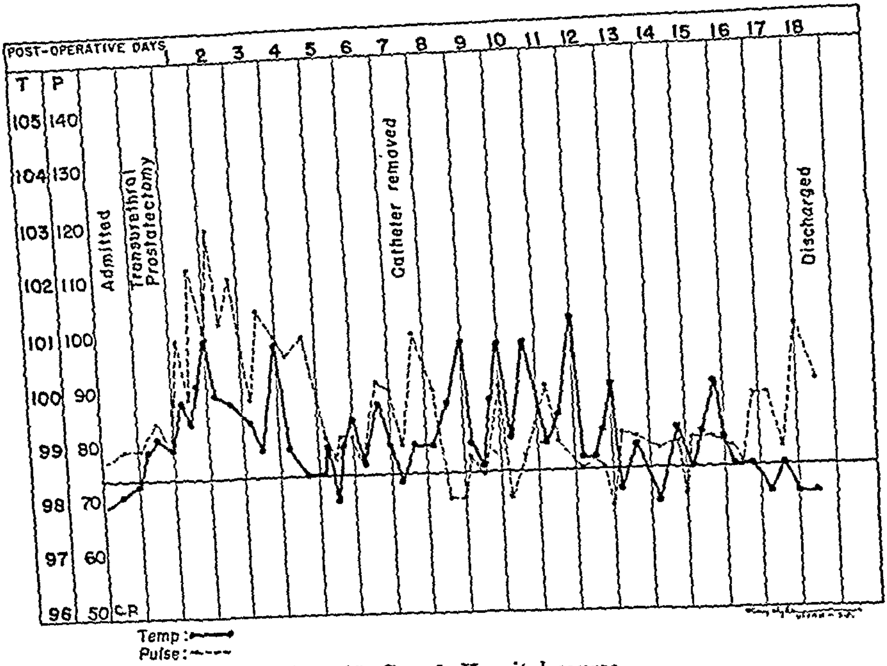

FIG. 15. Case 2. Hospital course

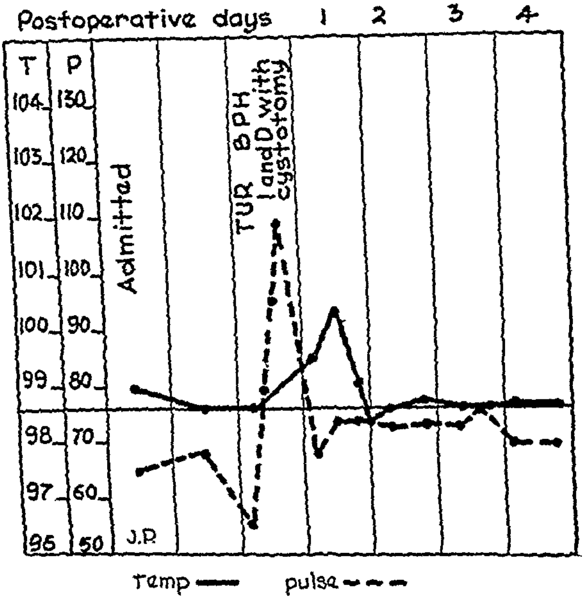

FIG. 16. Case 3. Hospital course

and tenderness. Resection was terminated. Because the urethral catheter did not drain freely over a period of 7 hours and local signs persisted, suprapubic drainage and closure of the opening were carried out. A urethral catheter was left in place postoperatively.

Case 4 (fig. 17): Patient W. K., white man. Age: 62 years. Lateral lobe intraurethral benign prostatic hypertrophy. No infection. Extensive extraperitoneal perforation, continued extravasation and uncontrollable bleeding. *Suprapubic drainage and cystostomy.* Recovery.

Left midprostatic capsule was perforated after removal of 28 gm. tissue. Postoperatively the patient immediately complained of suprapubic pain, and examination showed tenderness, rigidity and suprapubic swelling. On suprapubic exploration, extensive bloody periprostatic extravasation was found. Bleeding was controlled with a urethral bag catheter. Suprapubic cystostomy was performed as a safety measure.

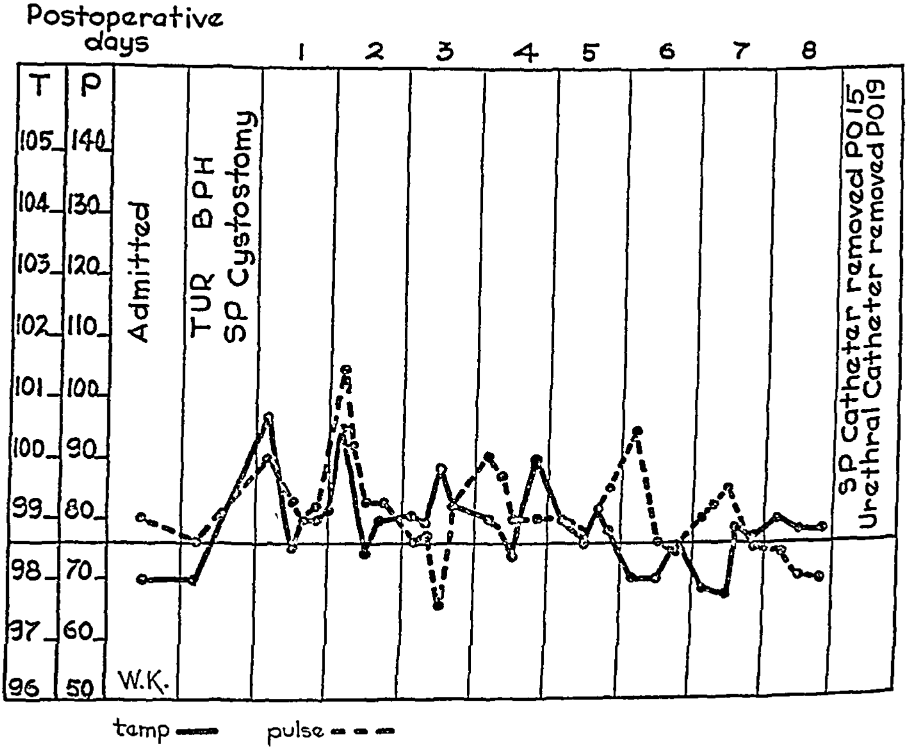

FIG. 17. Case 4. Hospital course

CONCLUSIONS

In the clinical management of urinary extravasation incident to transurethral resection, it is important to recognize that there is little danger from the isolated escape of uninfected urine into the tissues. Quantities of urine or irrigating fluid which escape during operations are comparatively innocuous and do not require open drainage.

When infection is present, however, extravasation may produce a toxic inflammatory reaction, and proper evaluation of this process is fundamental to rational treatment.

The employment of conservative treatment depends on the maintenance of free urethral catheter drainage. Evidence of continued urinary extravasation, bleeding, and persistent local signs of acute inflammation are indications for open operation.

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REFERENCES

Bailey, H. and Huddy, G. P. B.: Extravasation of urine with especial reference to periurethral abscess. Brit. J. Surg., 12: 183–191, 1924.
Bezza, P.: L'infiltrazione urinosa dal punto di vista sperimentale. Arch. ital. di chir., 41: 1–62, 1935.
Char, G. Y., Shih, H. E. and Yang, C. P.: Extravasation of urine. Chinese Med. J., 50: 807–820, 1936.
Kenyon, H. R.: Perforations in transurethral operations. J. A. M. A., 142: 798–802, 1950.
Wolfer, J. A.: Urinary extravasation. Surg., Gynec. & Obst., 26: 296–302, 1918.
Yasuda, S. and Sakabe, T.: On the toxicity of urine. Sei-I-Kai M. J., 60: 565, 1941. (Abstract: J. A. M. A., 117: 1745, 1941.)

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THE SURGERY OF INTERSEXUALS

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The treatment of congenital anomalies of the genitalia is a very important part of urology. Rarely, genital anomalies occur to such a degree that the sex of the child is in doubt. The presence of sexual organs of both sexes in the same individual constitutes intersexuality, and in intersexes, urologic examination is essential for determination of the extent of the anomalies, the sex of the child, and the prognosis as to social adaptation. In the past 8 years at the University of California Hospital, the urology staff studied 19 patients with severe intersexual anomalies. In 8 patients, the original diagnosis of sex was found to be incorrect, and in 6 of these, a most satisfactory change of sex was effected (table 1). The crucial diagnostic step was at times the simple one of identifying a testicle by palpation. In other cases, the diagnosis was only reached after laboratory, instrumental, and x-ray studies or by surgical exploration.

There are excellent procedures for correcting genital anomalies, but in the treatment of intersexes, the questions of what to correct and when to do it are difficult to answer unless the ultimate appearance and behaviour of the patient can be predicted. This depends upon knowledge of the pathological anatomy and pathological physiology of the various types of intersexes. Confusion in the surgical treatment of intersexuality arises from failure to appreciate that psychic sexuality is formed by upbringing and the reaction of the individual to environment and to physical appearance rather than by any innate developmental process. There is also no satisfactory clinical classification of intersexes.

Intersexuality may be either acquired or congenital. When acquired, it is caused by tumor or hyperfunction of the gonad or adrenal and its treatment is control of the primary process. If this can be done, the abnormality is reversible. When congenital, the cause is developmental, and the condition is irreversible. Treatment is directed toward the adaptation of the individual to our heterosexual society which requires that a person be either male or female. Such adaptation is dependent upon environmental conditioning, physical appearance, and genital function.

Many intersexes are conceivably adaptable to life as either sex, and some have adjusted their lives very well to the sex opposite to their true sex. These facts have led some authorities to advise deferring definitive treatment of intersexes until an age is reached where psychic sexuality develops.[1] The age at which this is supposed to occur is not clear, but is generally taken to be at or near puberty. Awaiting the development of psychic sexuality is an erroneous approach to the problem because, in humans, psychic sex has little genetic or endocrine basis and is determined almost entirely by environmental conditioning.[2, 3] Intersexes generally maintain the sex in which they are reared, no matter how poorly

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Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 11, 1950.

[1] Novak, E.: Congenital anomalies. Surg., Gynec. & Obst., 86: 247, 1948.

[2] Ellis, A.: Sexual psychology of human hermaphrodites. Psychosom. Med., 7: 108, 1945.

[3] Perloff, W. H.: Role of the hormones in human sexuality. Psychosom. Med., 11: 133, 1949.

suited they are to it physically, and it is usually inadvisable to effect a change of sex in adolescence or adulthood because of the many psychic conflicts engendered.[4] The younger the child, the easier it is to change the social sexual status. The correct approach to the problem is to determine sex early and to rear the child as a normal member of the sex into which he will best fit in adult life. The genital deformities should be corrected as well as possible at the earliest age practicable.

TABLE 1

DIAGNOSIS OF SEX AT BIRTH	AGE DIAGNOSIS OF SEX ESTABLISHED	COMMENT
	Female adrenal intersex	
1. Female	6 weeks	Adrenal insufficiency also
2. Male	6 weeks	Adrenal insufficiency also
3. Female	4 months	
4. Female	6 months	
5. Female	6 months	
6. Female	18 months	
7. Female	18 months	
8. Female	5 years	
9. Female	19 years	
10. Female	24 years	Erroneously pronounced male after laparotomy at age of 14 years
	Male intersex	
11. Male	1 year	
12. Intersex	1 year	Changed to male
13. Female	1 year	Changed to male
14. Intersex	18 months	Changed to male
15. Female	13 years	Changed to male
16. Female	19 years	Changed to male
17. Male	22 years	
	Female intersex-vaginal urethra type	
18. Male	3 years	Changed to female
19. Female	3 years	

Because genetic sex cannot be determined, the diagnosis of sex is based upon the type of gonads present. The occasional occurrence of testicular tissue in genetic females detracts from the validity of this concept. However, the nature of the gonads provides the basis for sex determination in law and religion and when properly evaluated in connection with other findings, is an accurate clinical guide to treatment. Medical treatment directed towards assumption of a sex opposite to that of the gonads is not indicated except when the attitude of the patient or his parents necessitates it or in special instances where insurmountable physical obstacles exist.

The mechanisms producing genital anomalies can be deduced through knowledge of embryology. However, the etiology of congenital intersexuality i known. As will be demonstrated later, some types of intersexuality appear

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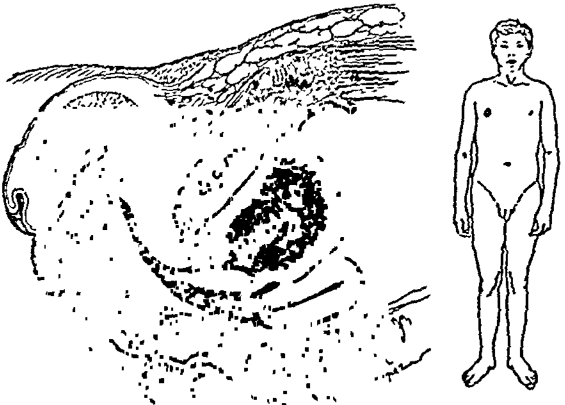
[4] Young, H. H.: Genital Abnormalities, Hermaphroditism, and Related Adrenal Diseases. Baltimore: Williams and Wilkins, 1937.

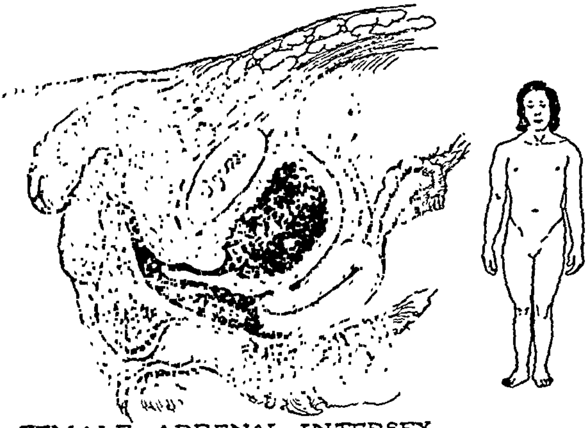


MALE INTERSEX CHARACTERISTICS

Undescended testis.
Imperfect masculine development of urogenital sinus.
Imperfect feminine development of Muellerian ducts.

Fig. 1

Figs. 1–5. Physical characteristics of intersexes. Typical genitalia are shown in diag and the typical adult appearance in figure sketches. There is considerable variatio genitalia and in habitus of individual male intersexes (fig. 1), and of individual gonadal i sexes (fig. 4). Individual members of other 3 groups do not vary greatly from finding shown (figs. 2, 3, 5).

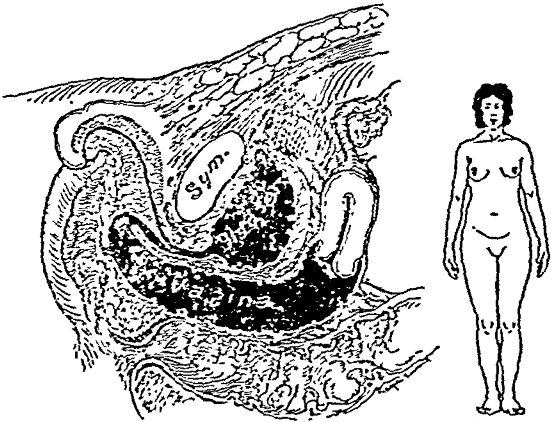


FEMALE ADRENAL INTERSEX CHARACTERISTICS

Normal ovaries and Muellerian duct derivatives.
Urogenital sinus masculinized by androgenic hyperfunction of adrenal cortex.

Fig. 2

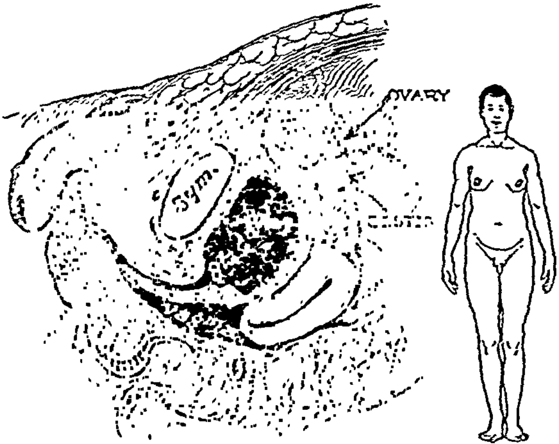
caused by influences affecting all the differentiating genital primordia and othe by purely developmental defects. Except in the case of the female adrenal inte sex, there is no evidence that hormones are in any way involved in the path genesis of the congenital deformities. Excellent papers in the etiology of intersexuality have been published recently by Moore,[5] and by de Vaal.[6]



FEMALE INTERSEX VAGINAL URETHRA TYPE
CHARACTERISTICS

Normal ovaries and adrenals.
Muellerian ducts imperfect in descent and fusion
Atypical masculinization of urogenital sinus

FIG. 3



GONADAL INTERSEX HERMAPHRODITE
CHARACTERISTICS

Ovotestes or ovary and testis.
Variable intersexual development of genitalia.

FIG. 4

Intersexes differ not only from the normal but from one another. Adequate data are available to permit classification of human congenital intersexes into five groups (figs. 1–5). The anatomical characteristics depicted in the diagrams are easily determinable at any age. The physical appearance of the adult may be predicted from the findings in childhood. Psychosexuality is environmentally determined and is not considered in the classification. Each group bears a superficial resemblance to the others but is actually distinct and greatly different.

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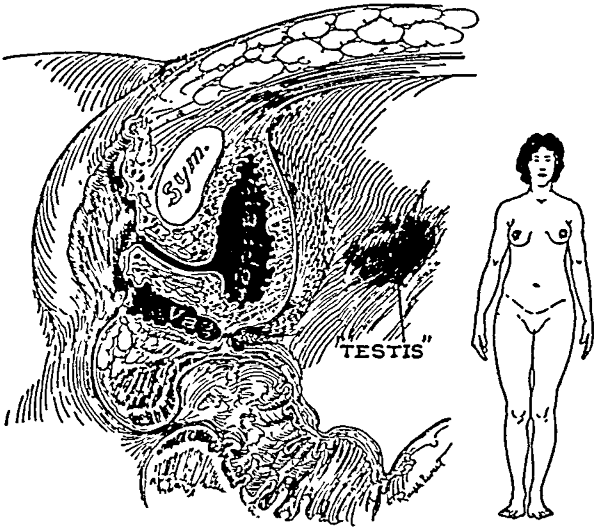
[5] Moore, C. R.: Sex endocrines in development and prepuberal life. J. Clin. Endocrinol., 4: 135, 1944.

[6] de Vaal, O. M.: Gonads, adrenals, and intersexuality. Gynaecologia, 128: 205, 1949.

MALE INTERSEX

The male intersex has a group of coordinated genital anomalies best explained by the action of a feminizing influence on the embryo.[7] In the order of frequency, these anomalies consist of hypospadias, impaired testicular descent, feminine development of the müllerian structures, and imperfect development of the structures of wolffian origin. There is considerable individual variation in the extent to which the various sexual structures are altered. The vagina usually connects with the urethra, but both the vaginal and urethral openings may be in the perineum. Individuals with minor degrees of hypospadias are usually not classified as intersexes but may be considered as a gradation between intersexuality and normalcy. Study of hypospadias shows that it is usual to find development of the uterovaginal tract and imperfect testicular descent in all but the mild cases (figs. 6, 7, 8). In perineal hypospadias, considerable development of the vagina and uterus will usually be present. Both the male and female genitalia are imperfectly developed. At birth, distinction between the male intersex and



ADENOMA TUBULARE GROUP
CHARACTERISTICS
Gonad resembling rudimentary testis.
No epididymis.
Failure of Muellerian duct development.
Normal female external genitalia.

FIG. 5

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[7] Howard, F. S.: Hypospadias with enlargement of the prostatic utricle. Surg., Gynec. & Obst., 86: 307, 1948.

a second group, the female adrenal intersex, may be impossible without exploration. However, at the age of 1 year, distinction is not difficult because the female adrenal intersex shows elevation of the 17-ketosteroid excretion and an advanced bone age.[8] These two tests give normal findings in all other congenital intersexes.

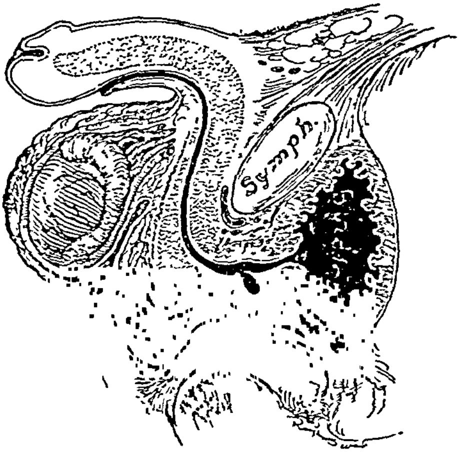

Fig. 6

Figs. 6–8. Study of patients with hypospadias shows a trend toward coordinated feminization affecting all genital structures. More marked hypospadias is, greater degree of impairment of testicular descent and greater development of uterovaginal tract.

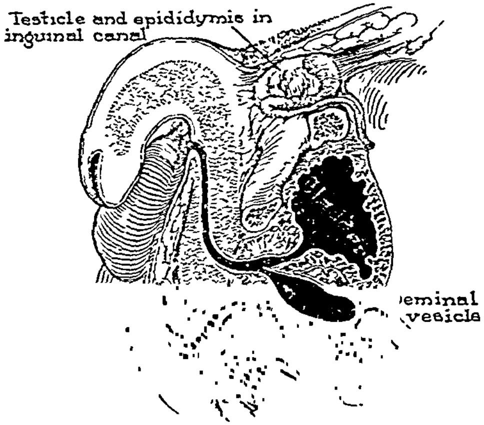

Fig. 7

If a testis and epididymis are clearly identified by palpation, it is safe to proceed with repair of the hypospadias; if not, exploration is advisable. The prognosis for masculine adjustment is excellent if the genital anomalies are satisfactorily corrected by surgery. No endocrine dysfunction is likely to develop unless the testicles cannot be brought down or are lost in the process.

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[8] Wilkins, L.: Abnormalities and variations of sexual development during childhood and adolescence. Advances in Pediatrics, 3: 159, 1948.

FEMALE ADRENAL INTERSEX

The female adrenal intersex is born with androgenic hyperfunction of the adrenal cortex which causes masculinization of the urogenital sinus. This condition is really a hormonal sex inversion, and the term intersex is applicable only in its broadest sense. In all recorded congenital cases, the adrenal disease has been hyperplasia, and tumor has never been found, but when a female is normal at birth and becomes masculinized later there is always a strong possibility of tumor.[9] The internal genitalia of the female adrenal intersex at birth are normal ovaries, oviducts, and uterus. The upper vagina is normal but the lower portion joins the urethra to form a common urogenital passage opening at the base of a markedly hypertrophied clitoris. The appearance is that of a perineal hypospadias. Although increased androgen production can often be detected by laboratory means in neonatal life, the 17-ketosteroid excretion is so low in these infants that significant positive findings beyond the limits of error of the test may not be obtained until the age of 6 to 12 months. Treatment of this intersex is completely unsatisfactory because the hyperfunctioning adrenals produce progressive virilization throughout life. There is no surgical or medical treatment to decrease the excess production of androgen or to neutralize its effects. The results of subtotal adrenalectomy have been particularly disappointing.

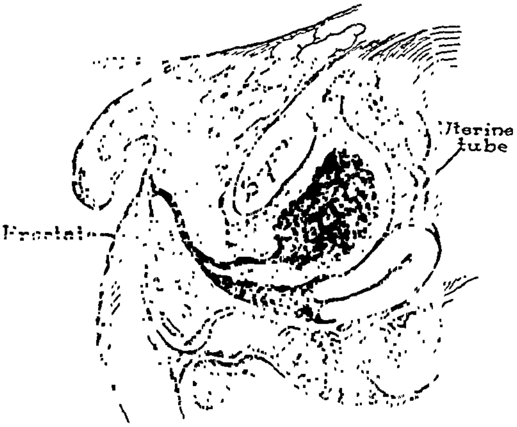

FIG. 8

The effects of excess androgen are manifested by early rapid skeletal growth and by the early appearance of pubic and axillary hair. The epiphyses fuse several years earlier than is normal and the usual height at maturity is in the neighborhood of five feet. Hirsutism, including the face, is prominent, and the scalp hairline recedes in masculine fashion. The internal genitalia remain infantile and there is little or no breast development. Because the tissues are those of a genetic female, they are incapable of becoming completely masculinized by androgen. The body build and external genitalia are therefore intersexual.[10] The upper extremities and chest are masculine in contour, but the waist and hips are feminine. Although the clitoris is markedly hypertrophied, it seldom attains the size of the average penis. The tragic hopelessness of converting these individuals into functioning females has caused some authorities to advise that the clitoris be made into a penis by a hypospadias repair and that they be reared as males. This solves the problem of hirsutism but creates an anomalous legal position and by no means guarantees social adjustment. A masculine psyche is readily developed if the change is made early enough, and coitus with females is possible although the phallus is small. In the case reported by Young, inability legally to marry a woman was the cause of suicide.[4] Despite the hair problem, it is better to rear these individuals as females.

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[9] Wilkins, L.: Feminizing and virilizing adrenal tumors. Classification of adrenal disorders. J. Clin. Endocrinol., 8: 122, 1948.

[10] Bayer, L. M.: Pseudohermaphroditism; a psychosomatic case study. Psychosom. Med., 9: 246, 1947.

Study of adults in this group reveals that most of them make a fairly satisfactory social adjustment as females, although they generally lead secluded introverted lives. Sexual drive is minimal and when present is directed toward the male. Marriage and coitus are infrequent. Surgery has little to offer. Although the diagnosis is evident by clinical study, exploratory laparotomy with ovarian biopsy is indicated because the diagnosis is almost certain to be doubted later unless this is done. Laparotomy is also indicated by the remote possibility of adrenal or ovarian tumor. The value of clitoridectomy is less than it might appear but is justifiable if the organ is annoying the child or her parents. Attempts to form a vaginal introitus in childhood fail because the excess male hormone causes rapid postoperative contracture, and in adult life this procedure is of no value unless coitus is contemplated.

An important aspect of adrenal intersexuality is the simultaneous occurrence of corticoadrenal insufficiency in 10 to 15 per cent of the cases.[8] This infantile Addison's disease is manifested in the first few weeks of life by vomiting, diarrhea, and failure to gain weight. Unless treated with sodium chloride and adrenal cortical extract, the condition is usually fatal. However, mild cases may be controlled by salt alone, even inadvertently, such as by changing the diet from human milk to cow's milk. In operating upon adrenal intersexes, the possibility of a complicating unrecognized Addison's disease must be borne in mind.

FEMALE INTERSEX: VAGINAL URETHRA TYPE

Female intersexes of the vaginal urethra type are very rare, but their recognition is of the utmost importance because of the adverse effect of the genital anomalies on the urinary tract.[11, 12, 13] This condition is best explained on the basis of a purely local developmental defect consisting of failure of early contact of the müllerian ducts with the urogenital sinus and locally uninhibited development of the genital tubercle. In contrast to the adrenal intersex, progressive masculinization is absent. The vaginal introitus is fused anteriorly forming a dense curtain of tissue in front of and partially obstructing the urethral meatus. The clitoris is hypertrophied, and sometimes a rudimentary supplementary

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[11] Blum, V.: Die Hypospadie der weiblichen Harnröhre. Monatsbericht f. Urol., 9: 522, 1904.

[12] Grubenmann, Ida: Eine sagittale Verdoppelung der weiblichen Harnröhre. Frankfurt. Ztschr. f. Path., 10: 101, 1912.

[13] Howard, F. S. and Hinman, F., Jr.: Female pseudohermaphroditism with supplementary phallic urethra. Report of two cases. J. Urol., 65: 439, 1951.

urethra courses through it. The ovaries and oviducts are normal, but the uterus and vagina show variable degrees of reduplication. Voiding occurs into the vagina producing an enormous megalovagina by hydraulic distention in fetal life. Urine pools in the vagina and dribbles out incontinently. A very small amount of each voiding comes through the rudimentary phallic urethra. Most children with this anomaly have died early from urinary obstruction and infection. Unless irreparable urinary tract damage has taken place, these patients can be cured surgically by enlarging the vaginal introitus perineally and resecting the redundant vagina transabdominally. In constructing the introitus, it is important to carry skin flaps from the labia down to the urethral meatus to prevent reformation of the anterior introital bridge. The clitoris should be amputated.

GONADAL INTERSEXES

Gonadal intersexes are the so-called true hermaphrodites and are characterized by the presence of an ovotestis in combination with an ovary or testis, bilateral ovotestes, or an ovary and a testis. There are only 40 to 50 recorded instances in the human.[4, 14, 15] In most of these cases ovotestes have been found rather than separate and distinct contrasexual gonads. The external genitalia vary from normal female to normal male but for the most part resemble those of the male intersex. When ovarian tissue is present, the physique and breast development are usually feminine, and menstruation usually occurs. There is strong agreement between psychic sex and the sex in which the individual is reared. The evidence indicates that most gonadal intersexes are the result of a masculinizing influence acting on the differentiating gonads of genetic females at an early stage of development. The normal undifferentiated ovary has a cortical portion which becomes the ovary proper and a medullary portion which becomes the rete ovarii. The ovarian medulla is capable of becoming a testis. This is significant in explaining the development of an ovotestis in intersexes and the occurrence of arrhenoblastomas in normal women.

In the treatment of gonadal intersexes, when one gonad is normal and the genitalia and other sexual characteristics are harmonious with the sex of the normal gonad, removal of the other gonad and appropriate genital plastic surgery is indicated. When bilateral ovotestes are present, the problem is more complex. It is rarely possible to remove all the ovarian tissue without entirely destroying the gonads. Placement of an ovotestis in the scrotum is unsatisfactory because the ovarian portion becomes cystic and painful, necessitating gonadectomy.[14, 16] The choice in bilateral ovotestis usually lies between castration and leaving the ovotestis in the abdomen. Because the secondary sexual characteristics are principally female, preference is given to surgical feminization of the external genitalia and a female social status. The testicular portion of an ovotestis appears to exert little contaminating influence.

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[14] McIver, R. B., Seabaugh, D. R. and Mangels, M., Jr.: True hermaphroditism: A report of two cases. J. Urol., 52: 67, 1944.

[15] Weed, J. C., Segaloff, A., Wiener, W. B. and Douglas, J. W.: True hermaphroditism. J. Clin. Endocrinol., 7: 741, 1947.

[16] Engle, E. T., Yeaw, R. C. and Lattimer, J. K.: True hermaphroditism: Supplementary report of a case. J. Urol., 56: 731, 1946.

ADENOMA TUBULARE GROUP

Adenoma tubulare is the name given to a rare testicular tumor consisting of immature seminiferous tubules and normal interstitial cells.[17] The same histology is found in the differentiated arrhenoblastoma of the ovary, and the same name is applied to this tumor. The term, adenoma tubulare group, is used in this classification of intersexes because the members of the group possess gonads which appear to be neither ovaries nor testes. However, the term is somewhat misleading because the peculiar gonadal structures are not necessarily neoplastic.

The individuals classified under this term have a typically feminine physique and external genitalia, but the gonads are indistinguishable histologically from immature testes.[17-24] There is also absence of the upper four fifths of the vagina and of the uterus and oviducts indicating failure of müllerian duct development. The vaginal introitus, labia, and clitoris, which are derived from the urogenital sinus, are normal. The gonads lie either at the normal position for ovaries or along the inguinal canal and differ from undescended testes in that epididymides are absent or rudimentary. Vasa deferentia, seminal vesicles, and prostate are absent. In adult life, the mammary glands are well-developed and the hair distribution is feminine except that the axillary and pubic hair are absent or sparse. The endocrine function of the gonads has not been fully studied, but it is known that their removal produces typical menopausal symptoms. The 17-ketosteroid excretion is within the normal range for females.[23] Individuals with this combination of anomalies have been considered either as genetic males with extreme feminization or as genetic females with total suppression of development of the ovarian cortex and müllerian ducts. The anatomy of the genitalia differs vastly from that of the male intersex where the degree of development of the structures of müllerian origin is proportional to the degree of feminization of the external genitalia. The etiology of the condition is best explained by the occurrence, in a genetic female, of a local developmental error consisting of complete müllerian duct and ovarian cortex inhibition with unihibited differentiation of the ovarian medulla. In some respects, it is closely related to the syndrome of ovarian follicular agenesis, where both the ovarian cortex and medulla fail to develop.[25]

Intersexuality is not suspected until the abnormal gonads are discovered during surgery performed for the complaint of inguinal hernia or congenital absence of the vagina. Both gonads are always abnormal and when they are removed a surgical menopause results. When they are left alone or transposed from the inguinal region to the pelvis they exert no adverse androgenic influence. Benign neoplastic enlargement has been reported to have developed in some cases.[20] Because these individuals are closely related to normal women in all other respects, intercourse is frequently desired and construction of an adequate vagina is indicated after maturity. When inguinal hernias are present they should be repaired. The best procedure to adopt in handling the gonads is not determined. In the adult there is a choice between castration with estrogenic substitution therapy and leaving the gonads in the pelvis, when frequent pelvic examinations should be done to detect the possible occurrence of tumor. In childhood, the advantage of preserving the gonads for their endocrine function outweighs the risk of malignant degeneration. A change of sex to male is completely out of the question anatomically.

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[17] Selye, H.: Ovarian tubular adenomas. Encylopedia of Endocrinology, Section IV, Vol. VII, pp. 75–82. Montreal: Richardson, Bond and Wright, 1946.

[18] Wagner, G. A.: Über hermaphroditismus verus. Zbl. f. gynäk., **51:** 1304, 1927.

[19] Cadiz, R. and Lipschütz, A.: Über einen Fall von Pseudohermaphroditismus masculinus. Arch. f. gynäk., **153:** 593, 1933.

[20] Novak, J.: Testicular tubular adenoma in two sisters. Am. J. Obst. & Gynec., **45:** 856, 1943.

[21] Bleyer, L. F.: Pseudohermaphroditism. Am. J. Surg., **76:** 448, 1948.

[22] Goldberg, M. B. and Maxwell, A. F.: Male pseudohermaphroditism. J. Clin. Endocrinol., **8:** 367, 1948.

[23] Ward-McQuaid, J. N. and Lennon, G. G.: Inguinal hernias, absence of uterus, and pseudohermaphroditism. Surg., Gynec. & Obst., **90:** 96, 1950.

[24] Fazen, L. E., Jr.: Female intersex. Wisc. M. J., **48:** 1077, 1949.

[25] del Castillo, E. B. de la Balze, F. A. and Agonz, J.: Syndrome of rudimentary ovaries with estrogenic insufficiency. J. Clin. Endocrinol., **7:** 385, 1947.

DISCUSSION OF SURGICAL TREATMENT

In congenital intersexes, surgery has its principal application in diagnosis and in the plastic construction of the external genitalia. Diagnostic surgery with gonadal biopsy is indicated in early childhood if doubt as to sex exists. On birth of an indeterminate intersex, the parents should be informed of the anomaly and be promised a decision by the second year of life. In exploration of an adrenal intersex, where the 17-ketosteroid excretion is elevated, a supraumbilical transverse incision or a long longitudinal incision should be made so that both the gonads and the adrenals may be exposed. X-ray examination, including perirenal insufflation, has not been proven to be superior to surgery in differentiating adrenal tumor from adrenal hyperplasia in young children. Where ovotestis is suspected, biopsy should be made to include an entire longitudinal segment of the gonad.

Construction of the penis in male intersexes is best begun in the second year of life. The primary aim of hypospadias surgery is correction of chordee. The use of preputial skin flaps admirably fulfills the purpose of covering the bare ventrum of the penis after removal of the incurvating bands of connective tissue from the corpora. Blair's method[26] of forming preputial flaps by longitudinal incision of the opened out foreskin adapts itself better to the treatment of severe degrees of hypospadias than the buttonhole technique of Nesbit.[27] In perineal hypospadias, there is a midline longitudinal tract of smooth, hairless skin between the two halves of the scrotum which is sometimes wide enough for construction of that portion of the urethra. Frequently scrotal rugae encroach so close to the midline that it is evident that hair will be included in the urethra. The area should then be widened at the time of straightening the penis by the transfer of a split-thickness graft from a relatively hairless area of the body, such as the inner surface of the upper arm. At subsequent stages, first the perineal portion of the urethra and then the penile portion are constructed. There is usually not enough penile skin to permit formation both of the urethra and its external covering by the Thiersch method. The external covering is best supplied by scrotal flaps[26, 28] or by a scrotal tube pedicle.[29] The urethra should be made sufficiently large that postoperative dilatation will be unnecessary. Construction of the urethra distal to the coronal sulcus adds little to the functional and cosmetic result and greatly increases the incidence of stricture and fistula. The use of free inlay grafts to form the penile urethra is usually unnecessary, and has the disadvantage of possible longitudinal contraction when applied to young children. The danger of longitudinal contraction appears less if the penis is already fully developed or if a free inlay graft is used to form only the perineal portion of the urethra.[30]

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[26] Blair, V. P., and Byars, L. T.: Hypospadias and epispadias. J. Urol., 40: 814, 1938.
[27] Nesbit, R. M.: Plastic procedure for correction of hypospadias. J. Urol., 45: 699, 1941.

The problem of undescended testicle is far from solution. Watchful waiting, hormone treatment, and surgery are all useful in the treatment of this condition, but there is no method of producing uniformly satisfactory results. The pathological anatomy and life history of male intersexes give little encouragement of success from expectant or hormone treatment. Except when the testicles can be brought easily into the scrotum manually or when one testicle is fully descended, awaiting spontaneous descent at puberty is contraindicated. Orchiopexy should be performed before the age of 11, but there is no objection to a reasonable trial of endocrine therapy. When the testicles are intra-abdominal and whenever it is difficult to obtain adequate lengthening of the spermatic vessels, the procedure of Cabot[31] is particularly useful. This consists of forming an artificial tunica vaginalis testis with a peritoneal cuff and bringing the testicle only to the external ring. In several months, sufficient lengthening of the spermatic vessels will occur to allow placement of the testicle in the scrotum by a second operation.

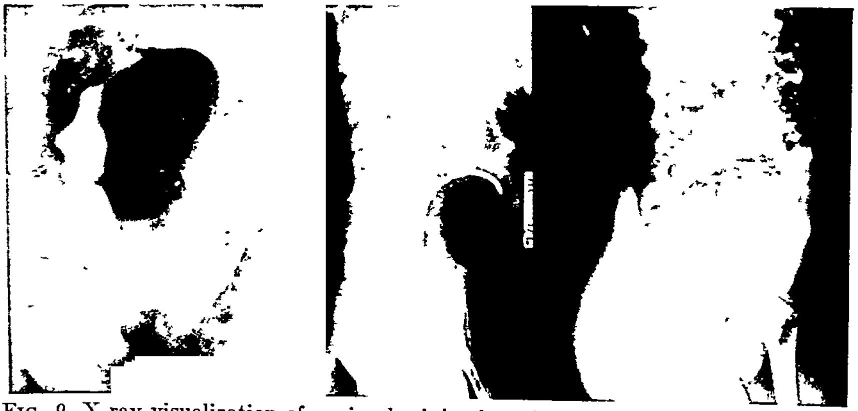

FIG. 9. X-ray visualization of vagina by injection of a radioopaque salt. From left to right are shown colpograms of male intersex, aet 19 years, female adrenal intersex, aet. 2 months, and female intersex of vaginal urethra type, aet. 3 years. In the latter two, bladder has been filled with air for contrast.

The study of vaginal abnormalities in both sexes is greatly facilitated by cystoscopy and by contrast x-ray examination (fig. 9). A vagina is common in

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[28] Cecil, A. B.: Repair of hypospadias and urethral fistula. J. Urol., 56: 237, 1946.

[29] Wehrbein, H. L.: Hypospadias. J. Urol., 50: 335, 1943.

[30] McIndoe, A. H.: The treatment of hypospadias. Am. J. Surg., 38: 176, 1937.

[31] Cabot, H.: The treatment of abdominal cryptorchidism. J. Mt. Sinai Hosp., 4: 596 1938.

male intersexes and a uterus may be present. When a uterus is found, however; the intersex is usually female. In the male, the vagina and uterus should not be removed unless there is evidence that they are causing disability. In constructing a urethra in these cases, the vaginal orifice may be safely incorporated in the urethra as shown by Cecil.[32] Except in the vaginal urethra type of female intersex where early surgery is essential to preservation of renal function, vaginal surgery in the female should be deferred until maturity because of the necessity of keeping the vagina dilated either manually or by coition.

When congenital intersexuality occurs, the possibility of subsequent pregnancies resulting in the birth of similarly abnormal children is frequently brought up by the parents. Study of the family history of intersexuals suggests a familial tendency which is strong in the case of adrenal intersexes but slight in the other types. The mother of a male intersex may safely risk other pregnancies with the expectation of normal children. However, when a woman has given birth to an adrenal intersex, her subsequent offspring are very apt to be similarly affected.

SUMMARY AND CONCLUSIONS

Acquired intersexuality is caused by endocrine dysfunction resulting from tumor or hyperplasia of the adrenals or gonads. The treatment is that of the causative lesion.

Congenital intersexuality is a developmental anomaly of undetermined etiology. It is not caused by tumor, nor is it related primarily to endocrine dysfunction except in the female adrenal intersex.

Treatment is based upon early diagnosis and is directed towards optimal adaptation of the individual to society. Early surgical correction of genital anomalies, whenever possible, is fundamental. Awaiting the development of sex consciousness before beginning definitive treatment is a tragic mistake because psychic sex is formed primarily by environment and is difficult to change.

Five groups of congenital intersexes are described, and their treatment is discussed.

a. The male intersex has a combination of anomalies usually including hypospadias, undescended testicles, and some degree of development of the uterovaginal tract. The penile and testicular deformities should be corrected in childhood, but it is usually unnecessary to remove the uterus or vagina.

b. The female adrenal intersex has normal internal genitalia but the external genitalia are masculinized by androgenic hyperfunction of the adrenals beginning in fetal life. Hyperandrogenism is persistent and masculinization is always progressive but never complete. There is no satisfactory treatment for the adrenal hyperfunction nor for its effects upon the patient. Plastic surgery and adrenal surgery are of little value. *The occurrence of a feeding problem in an infant with abnormal genitalia is virtually pathognomonic of adrenal androgenic hyperfunction complicated by corticoadrenal insufficiency.*

c. The female intersex of the vaginal urethra type is characterized primarily by a female urethra opening into the vagina against the inner aspect of a bridge of tissue completely closing the anterior portion of the introitus. Early surgical enlargement of the vaginal orifice is urgently required because of the grave effect of the anomaly on the entire urinary tract.

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[32] Cecil, A. B.: Surgical management of vagina in male construction in hermaphrodites. J. Urol., **62:** 709, 1949.

d. Gonadal intersexes have both ovarian and testicular tissue. Their treatment is an individual problem. Ovotestes should not be placed in the scrotum.

e. The adenoma tubulare group of intersexes consists of individuals with a female habitus and external genitalia but with gonads histologically indistinguishable from undescended testes. This group is frequently confused with the male intersex but differs strikingly by the absence of structures derived from the müllerian and wolffian ducts. Members of the adenoma tubulare group should be treated as females. The peculiar gonads do not cause virilization and their removal produces a surgical menopause.

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STUDIES IN GENERAL BIOLOGY OF SPERM: EXPERIMENTAL PRODUCTION OF SPERMATIC GRANULOMA

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More information about the general biological properties of sperm is needed to shed light on certain problems in the study of infertility. A hitherto unexplored avenue of attack may have been opened by the observations of Steinberg and Straus and Friedman and Garske that the interstitial tissues respond to the extravasation of sperm with a granulomatous reaction. The provoking by living cells of an inflammatory response of the type usually elicited by infectious agents or foreign materials seemed worthy of further investigation.

It appeared possible that the irritant property of the sperm cells responsible for the formation of the granuloma might be related in some way to the specialized functions of the male gamete. If this were so, study of this property could conceivably give objective data as to the health of the spermatic elements and possibly be an index of their fertility.

In order to study the phenomenon more satisfactorily it was deemed necessary to produce the granulomas experimentally in a suitable animal. In this paper their successful production in rats is being reported.

METHODS

Thirty adult male albino rats of the Wistar strain were used. In all animals the vasa deferentia were severed and the open cut ends implanted in either the scrotal wall or the abdominal cavity and retroperitoneum. In half of the animals the testes were removed from the scrotum, either at the time of the resection of the vasa or in a preliminary operation 3 to 4 weeks before severance of the vasa, and fixed in the abdominal cavity. Six combinations of operative procedures were used (fig. 1) with 5 animals in each group.

RESULTS

There was dilatation of the epididymis in many of the animals, resulting in a lesion resembling spermatocele in man. In some of the dilated ducts the inspissated contents were surrounded by an inflammatory granulomatous wall. At the ends of the severed ducts granulomas had formed. Grossly these were evident as yellow nodular masses or cysts up to 0.5 cm. in the greatest diameter. Microscopically the granulomas consisted of a central pool of sperm and other material surrounded by a wall of histiocytes or macrophages. There was little stainable fat in these granulomas, although some lipoid material was stained in sections of the abscesses and suture granulomas encountered in an occasional rat.

The granulomas were present in most of the animals whose testes had been left in the scrotum and whose vasa had been implanted in the scrotal wall. Some

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Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 9, 1950.

granulomas had formed about the ends of the intraperitoneal vasa, but in several of the rats whose vasa had been thus transplanted, the testes had undergone degeneration and no extravasation or granuloma formation had resulted. The testicular damage was attributed to interference with the blood supply at operation.

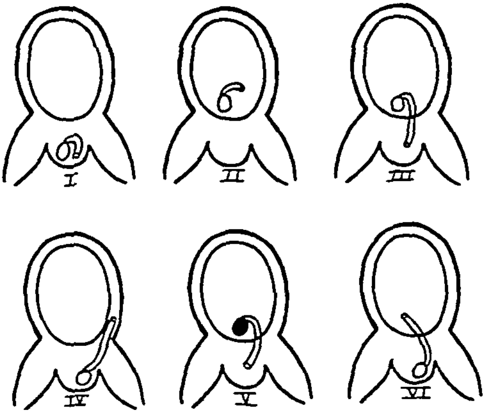

FIG. 1. Operative procedures. *I*, Testis left in scrotum; vas implanted in scrotal wall. *II*, Testis transplanted to abdomen; vas placed in abdominal cavity. *III*, Testis transplanted to abdomen; vas implanted in scrotal wall at same time. *IV*, Testis left in scrotum; vas implanted in retroperitoneum. *V*, Testis transplanted to abdomen; vas implanted in scrotal wall 1 month later. *VI*, Testis left in scrotum; vas placed in abdominal cavity.

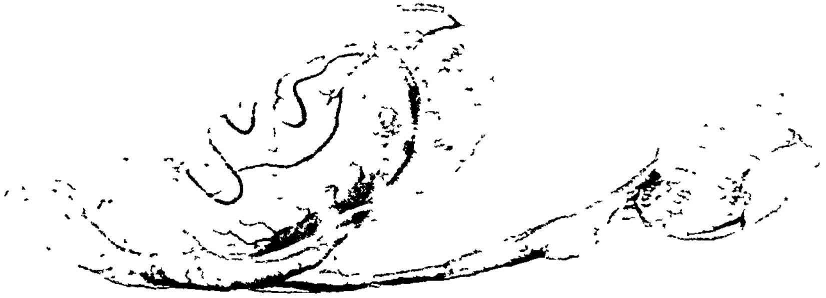

FIG 2. Granulomatous sac at resected end of vas 3 weeks after vas was placed in abdomen.

In the group in which the testes had been placed in the abdomen, only a few small granulomas were found about the cut ends of the vasa and they were all encountered in the sub group in which the vasa had been opened at the same time that the testes were relocated and in which the testes were not yet atrophic at the time of implantation of the vasa. No granulomas were found in the sub group in which the testes had been placed within the abdomen for a few weeks prior to cutting the vas and in which the testes had been atrophied by the time the vasa were opened. See figures 2–7.

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STUDIES IN GENERAL BIOLOGY OF SPERM: EXPERIMENTAL PRODUCTION OF SPERMATIC GRANULOMA

MURRAY RUSSELL AND NATHAN B. FRIEDMAN

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More information about the general biological properties of sperm is needed to shed light on certain problems in the study of infertility. A hitherto unexplored avenue of attack may have been opened by the observations of Steinberg and Straus and Friedman and Garske that the interstitial tissues respond to the extravasation of sperm with a granulomatous reaction. The provoking by living cells of an inflammatory response of the type usually elicited by infectious agents or foreign materials seemed worthy of further investigation.

It appeared possible that the irritant property of the sperm cells responsible for the formation of the granuloma might be related in some way to the specialized functions of the male gamete. If this were so, study of this property could conceivably give objective data as to the health of the spermatic elements and possibly be an index of their fertility.

In order to study the phenomenon more satisfactorily it was deemed necessary to produce the granulomas experimentally in a suitable animal. In this paper their successful production in rats is being reported.

METHODS

Thirty adult male albino rats of the Wistar strain were used. In all animals the vasa deferentia were severed and the open cut ends implanted in either the scrotal wall or the abdominal cavity and retroperitoneum. In half of the animals the testes were removed from the scrotum, either at the time of the resection of the vasa or in a preliminary operation 3 to 4 weeks before severance of the vasa, and fixed in the abdominal cavity. Six combinations of operative procedures were used (fig. 1) with 5 animals in each group.

RESULTS

There was dilatation of the epididymis in many of the animals, resulting in a lesion resembling spermatocele in man. In some of the dilated ducts the inspissated contents were surrounded by an inflammatory granulomatous wall. At the ends of the severed ducts granulomas had formed. Grossly these were evident as yellow nodular masses or cysts up to 0.5 cm. in the greatest diameter. Microscopically the granulomas consisted of a central pool of sperm and other material surrounded by a wall of histiocytes or macrophages. There was little stainable fat in these granulomas, although some lipoid material was stained in sections of the abscesses and suture granulomas encountered in an occasional rat.

The granulomas were present in most of the animals whose testes had been left in the scrotum and whose vasa had been implanted in the scrotal wall. Some

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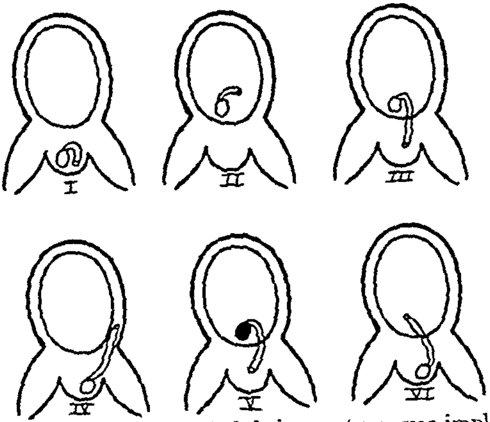
granulomas had formed about the ends of the intraperitoneal vasa, but in several of the rats whose vasa had been thus transplanted, the testes had undergone degeneration and no extravasation or granuloma formation had resulted. The testicular damage was attributed to interference with the blood supply at operation.



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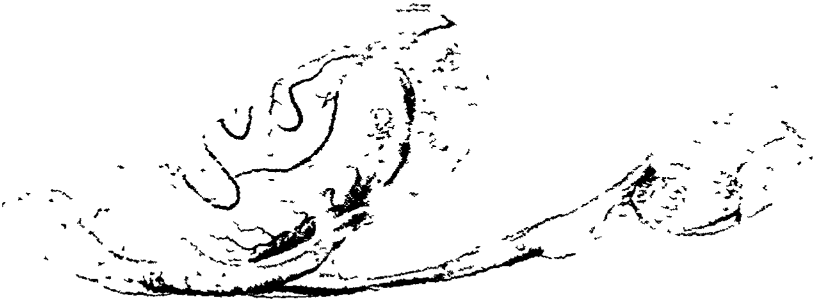

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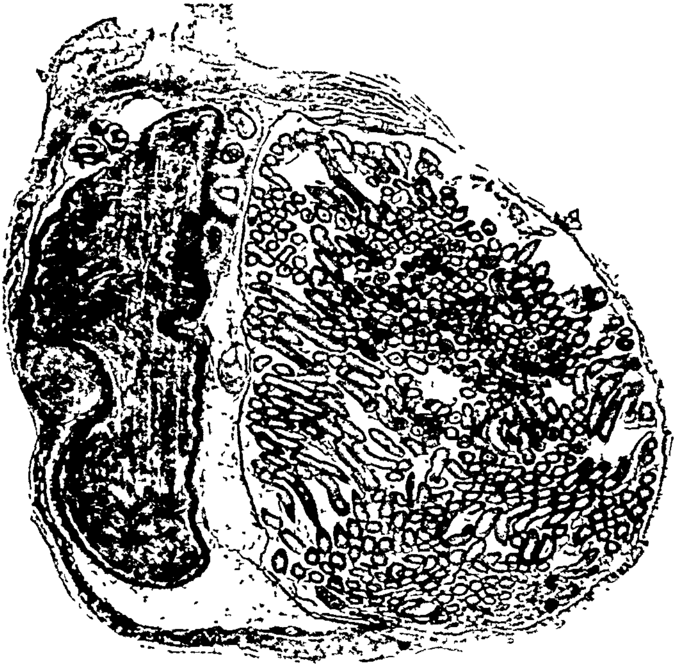

FIG. 3 Low power view (10 times) of cross section of scrotum and contents 2½ weeks after implantation of vas into scrotal wall. Vas can be seen surrounded by granulomatous mass.

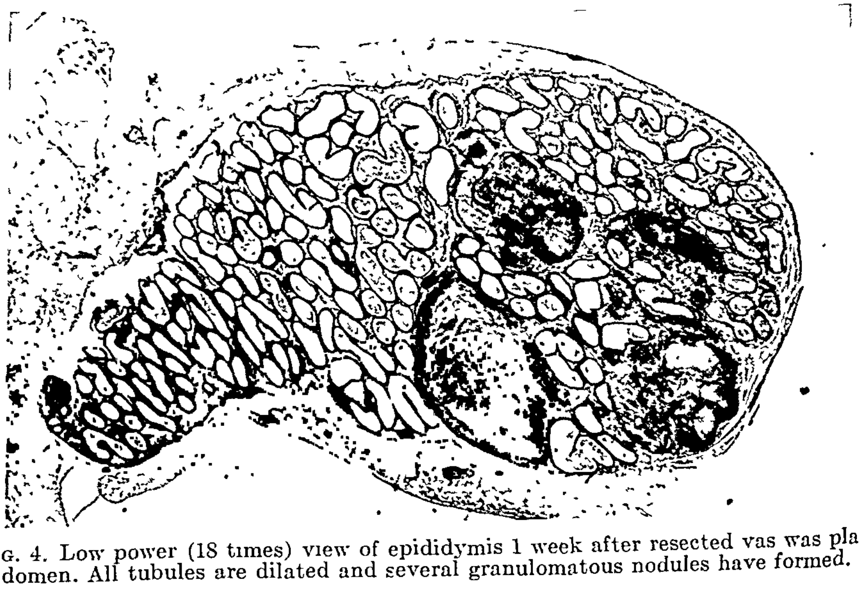

FIG. 4. Low power (18 times) view of epididymis 1 week after resected vas was placed in abdomen. All tubules are dilated and several granulomatous nodules have formed.

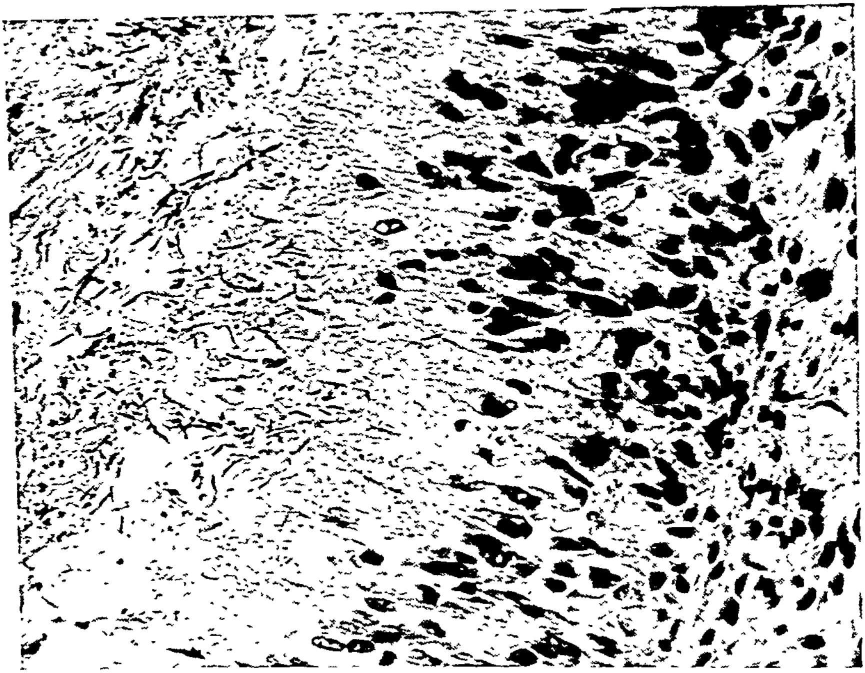

FIG. 5. High power (240 times) view of edge of a granulomatous mass. Pool of sperm is walled off by a palisade of histiocytes. Same animal as in figure 3.

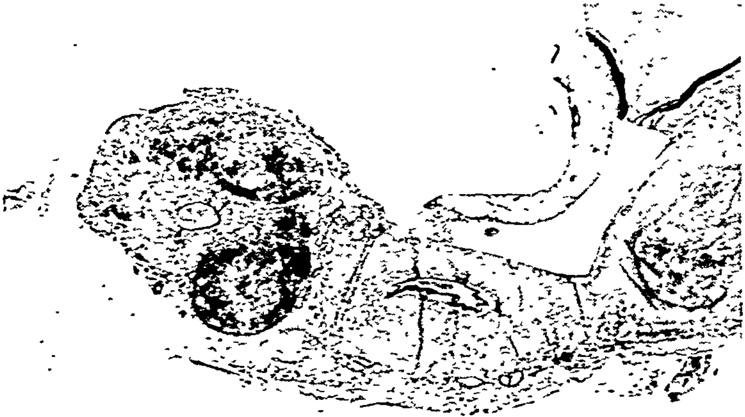

FIG. 6. Microscopic view (15 times) of spermatic granuloma surrounding resected end of vas. Testis left in scrotum. Compare with figure 7.

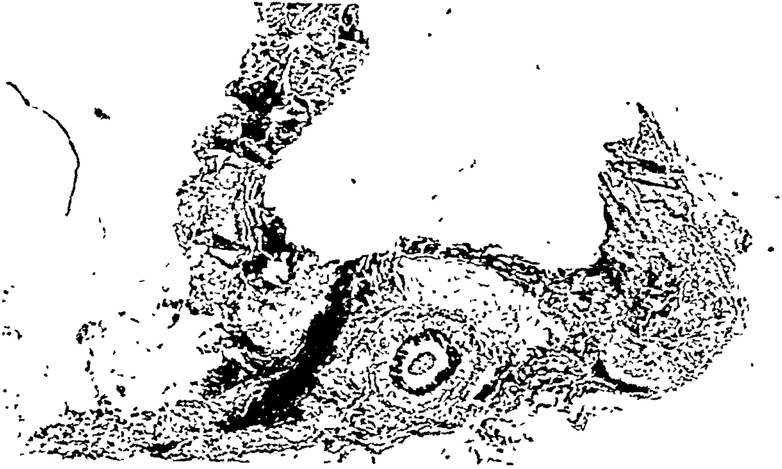

FIG. 7. Microscopic view (15 times) of resected end of vas after intra-abdominal transfer of testis. No granuloma has formed. Compare with figure 6.

DISCUSSION

Granulomas of the type described are commonly encountered as a reaction to irritating materials. Although the negative fat stains make it improbable that the spermatic granuloma is essentially a lipogranuloma, it is still possible that bound fat or a comparable substance in the sheath of the sperm cell may be responsible for the inflammatory response.

Is the motility of living sperm the provocative factor, or is it a specific chemical substance such as the nucleoprotein in which the sperm head is so rich? The absence of the reaction in the animals whose testes had been rendered atrophic makes it appear probable that the granuloma is due to the living sperm themselves or some associated material.

Spermatic granulomas may be of greater clinical significance than has hitherto been thought. Bayle's observation of "microcysts" along the vasa suggests the possibility that spermatic granulomas may be either primary or secondary etiologic factors in some cases of obstructive azoospermia.

SUMMARY

Spermatic granulomas comparable to those described in man have been produced in rats. The factors responsible for the histiocytic response to extravasated sperm are still unknown. Study of these factors might be useful in investigating fertility and an experimental approach to the problem is now possible.

Photographic illustrations were made by Mr. Dale Gillette.

9615 Brighton Way, Beverly Hills, Calif.

REFERENCES

BAYLE, H.: Masculine sterility latero-lateral-epididymo-deferens anastomosis in azoospermia by obliteration. Urol. & Cutan. Rev., **54:** 129–135, 1950.

FRIEDMAN, N. B. AND GARSKE, G. L.: Inflammatory reactions involving sperm and seminiferous tubules: Extravasation, spermatic granulomas and granulomatous orchitis. J. Urol., **62:** 363–374, 1949.

GREEN, W. W.: Chemistry and cytology of sperm membrane of sheep. Anat. Rec., **76:** 455–473, 1940.

MAYER, D. T. AND THOMAS, L. E.: The proteins of mammalian spermatozoa. Fed. Proc., **6:** 275, 1947.

STEINBERG, J. AND STRAUSS, R.: Sperm invasion of epididymis. J. Urol., **57:** 4[illegible]

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MARCH HEMOGLOBINURIA

ROBERT T. PLUMB

March hemoglobinuria is a condition in which physical exertion in the upright position gives rise to the passage of red urine containing hemoglobin in solution. This was first recognized following an Army march, hence the name "March." It is the only one of the hemoglobinurias which does not indicate serious systemic disease.

March hemoglobinuria occurs exclusively in healthy young adult men and is precipitated by walking or running but not by other types of physical exertion. It does not seem to be related to chilling, fever, sleep, hyperventilation, or local hemostasis. There is no familial or racial inclination to the disease, and no associated disease, or related physical abnormality which predisposes to it.

This type of hemoglobinuria is essentially asymptomatic; only a few patients report symptoms at the time the red urine occurs. An occasional cough, cramping in the abdomen, lumbar pain, or feeling of fatigue may be present. The hemoglobinuria lasts for a few hours and occasionally for a few days. The only physical signs reported have been the increase in the size of the spleen in 1 case and an increase in the size of the liver in 2 cases. There is no specific laboratory test for this disease.

The urine appears red and the color is proven to be hemoglobin by the benzidine and spectroscopic examinations. The 576 mu absorption band differentiates this from myoglobin (581 mu) and methhemoglobin (630 mu).[1] The urinary findings vary from the presence of no albumin to 4 plus albumin and from none to as many as 20 to 30 red blood cells per high power field. Approximately 6 to 40 cc blood is hemolyzed with an attack. The only positive finding in the blood has been the constant presence of hemoglobinemia during a paroxysm of hemoglobinuria. The pyelographic findings have all been essentially normal.

March hemoglobinuria is self-limited and recovery usually occurs without treatment within from a few months to one or two years. Occasionally it may last longer: in some cases occasional attacks have occurred for 7 years, and in one instance for 20 years.

The history of march hemoglobinuria, from the time of Fleischer in 1881 until 1940, has been carefully reviewed by Gilligan and Blumgart.[2] Since that time various case reports have appeared in the American, British, and Canadian literature As far as can be determined, this is the sixty-first case to be recorded.[3-15]

Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 11, 1950.

[1] Anson, M. L., Barcroft, J., Mirsky, A. E. and Oinuma, J.: On correlation between the spectra of various haemoglobins and their relative affinities for oxygen and carbon monoxide. Proc. Roy. Soc. London, Series B, 97: 61, 1924.

[2] Gilligan, D. R. and Blumgart, H. L.: March hemoglobinuria. Medicine, 20: 241–395, 1941.

[3] Gilligan, D. R., Alteschulte, M. D. and Katersky, E. M.: Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions. J. Clin. Invest., 20: 177–187, 1941.

[4] Gilligan, D. R., Alteschulte, M. D. and Katersky, E. M.: Physiologic intravascular

CASE REPORT*

An 18 year old male athlete was seen on March 21, 1949 complaining of red urine. He had been in track competition since September 1948. Recently, he had extended his usual one-mile run to four or five-mile runs. After four such runs at weekly intervals he passed dark urine which was present for 12 hours.

A mild cough, mild abdominal cramps, and general slightly under par feeling, were the only other presenting symptoms following the exercise. No other urinary symptoms were present. There were no chills or fever and no history of venereal disease. The past history and familial history were noncontributory.

The physical examination revealed a slender, asthenic individual with good posture and not apparently ill. The blood pressure was 118/80, the pulse rate 68, the temperature 98.6F. The head was normal. The chest was normal in shape, and the lungs were clear to percussion and auscultation. The left border of cardiac dullness was 7½ cm. to the left of the midsternal line in the 5th interspace; normal sinus rhythm was present and there were no murmurs. The musculature of the abdomen was exceptionally well-developed; otherwise all findings were normal and there was no enlargement of the liver or spleen. The external genitalia were without disease. The anal sphincter tone was good. The prostate was small and of fibrous consistency.

The urine at the time of first examination was clear yellow in color. The specific gravity was 1.018. No albumin, sugar, leukocytes, erythrocytes, casts, or organisms were present. The prostatic fluid was normal.

Blood examination revealed a hemoglobin concentration of 14 gm, 4,800,000 red blood cells, and 8,900 leukocytes of which 68 per cent were polymorphonuclears, 30 per cent lymphocytes, and 2 per cent monocytes. The Wassermann test was negative.

A roentgenogram of the kidney, ureter and bladder areas and excretory urograms were normal. Minimal scoliosis was present.

In an attempt to prove the diagnosis in this patient, we were fortunate in

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hemolysis of exercise; hemoglobinemia and hemoglobinuria following cross country runs. J. Clin. Invest., **22:** 859–869, 1943.

[5] Palmer, R. A. and Mitchell, H. S.: March hemoglobinuria. Canad. M. A. J., **49:** 465–472, 1943.

[6] Makin, M.: Case of march hemoglobinuria. British Med. J., **1:** 844, 1944.

[7] Bryce, L. M.: March hemoglobinuria; description of features of this condition and report of a case. Med. J. Australia., **2:** 48–52, 1944.

[8] Hobbs, R. E.: March hemoglobinuria; report of 2 cases. Am. J. Clin. Path., **14:** 485–488, 1944.

[9] Lindahl, W. W. and Fetter, M. E.: March hemoglobinuria; report of 2 cases. J. Urol., **53:** 805–807, 1945.

[10] Flemings, R. G. and Kinsman, J. M.: March hemoglobinuria. South. Med. J., **38:** 739–742, 1945.

[11] Bell, A. M.: March hemoglobinuria. Canad. Med. Assoc. J., **57:** 43–46, 1947.

[12] Ross, J. F.: Hemoglobinuria and hemoglobinemia. New Eng. J. Med., **233:** 691–693; 732–737; 766–771, 1945.

[13] Lowbury, E. J. L. and Blakely, A. P. L.: Exertion hemoglobinuria; case report. Brit. Med. J., **1:** 12–13, 1948.

[14] Kurz, E. R. H.: March hemoglobinuria. Brooklyn Hosp. J., **6:** 91–94, 1948.

[15] Lubran, M. and Sakula, J.: March hemoglobinuria. Lancet, **1:** 435–439, 1949.

* The author is indebted to Donald A. Wilson, Ph.D., Mercy Hospital, San Diego, Calif. for his assistance in doing the chemical analyses.

being able to reproduce the condition for study. Urine and blood specimens were obtained before and hourly for three hours after he ran one mile in 5 minutes and 15 seconds.

Figure 1 shows the plasma levels. The blood plasma level was above the normal of 5 mg. immediately and for the three hours following exercise. Figure 2A shows that the urine specimens were spectroscopically positive in the immediate and first hour specimens only. This tends to prove that the renal threshold for hemoglobin was between 45 and 75 mg. per cent. In normal individuals, when hemoglobin is injected intravenously, urine hemoglobin does not appear until a level in plasma of 100 mg. per 100 cc is reached.[3] The albumin (grade 1) and absence of erythrocytes are in keeping with similar findings in other reported cases.

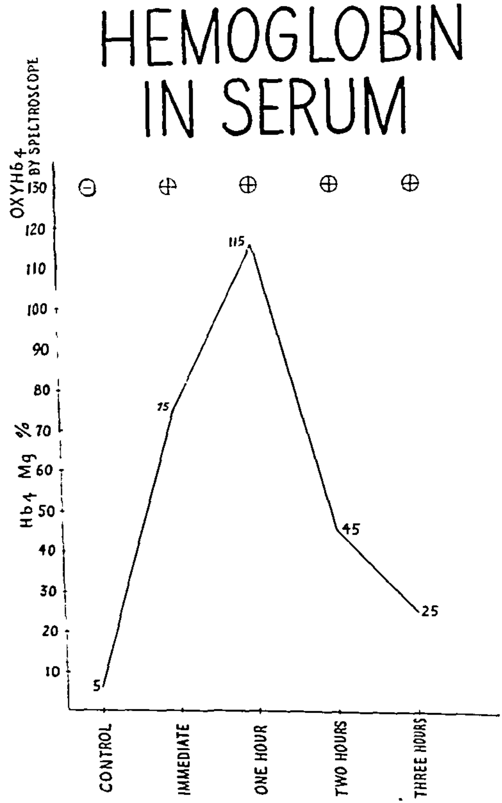


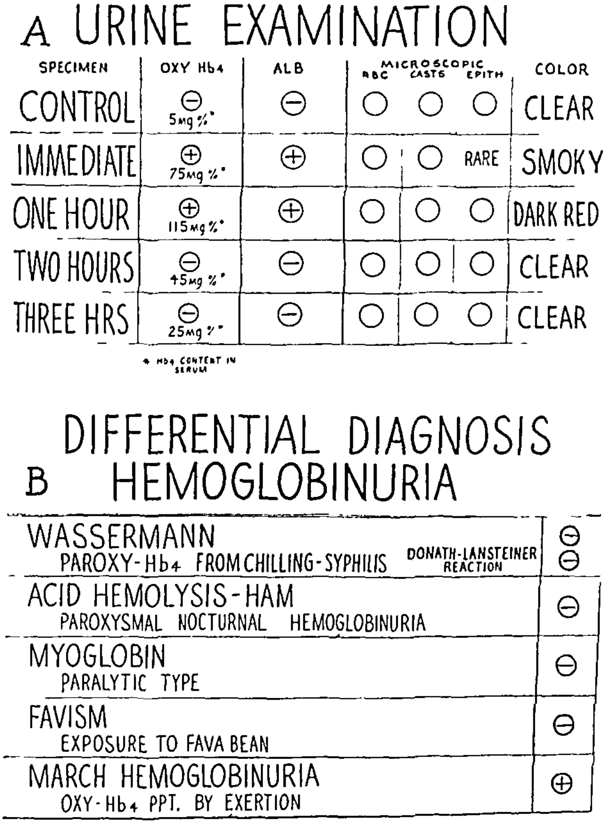
Fig. 1

The differential diagnosis in this benign disease is the important point. Fresh urine which is red, pink or black may owe its color to hematuria, hemoglobinuria, or from some pigment-producing substance which has been ingested or injected. Positive benzidine or guaiac tests without erythrocytes indicate free hemoglobin or myoglobin. Hemoglobin and myoglobin are differentiated by a spectroscopic examination.

The hemoglobinurias are divided into two main types: the endogenous and exogenous.

ENDOGENOUS

Paroxysmal hemoglobinuria from chilling, syphilitic type. The hemoglobinuria in this syndrome is induced by exposure to cold. A period of 10 minutes of chilling the hands and feet in ice water is enough. These people have either clinical syphilis or positive blood tests for syphilis. The presence of specific cold lysins is proved by the Donath-Landsteiner reaction. All other types of paroxysmal hemoglobinurias have negative Donath-Landsteiner tests. Adequate antileutic treatment usually controls attacks. There are no interval attacks.



A URINE EXAMINATION

SPECIMEN	OXY Hb4	ALB	MICROSCOPIC RBC	 CASTS	 EPITH	COLOR
CONTROL	⊖ 5mg %*	⊖	○	○	○	CLEAR
IMMEDIATE	⊕ 75mg %*	⊕	○	○	RARE	SMOKY
ONE HOUR	⊕ 115mg %*	⊕	○	○	○	DARK RED
TWO HOURS	⊖ 45mg %*	⊖	○	○	○	CLEAR
THREE HRS	⊖ 25mg %*	⊖	○	○	○	CLEAR

* Hb4 CONTENT IN SERUM

DIFFERENTIAL DIAGNOSIS
B HEMOGLOBINURIA

WASSERMANN PAROXY-Hb4 FROM CHILLING-SYPHILIS DONATH-LANSTEINER REACTION	⊖ ⊖
ACID HEMOLYSIS-HAM PAROXYSMAL NOCTURNAL HEMOGLOBINURIA	⊖
MYOGLOBIN PARALYTIC TYPE	⊖
FAVISM EXPOSURE TO FAVA BEAN	⊖
MARCH HEMOGLOBINURIA OXY-Hb4 PPT. BY EXERTION	⊕

FIG. 2

Paroxysmal nocturnal hemoglobinuria, Marchiafava-Micheli disease. This disease of unknown etiology begins insidiously with later stages characterized by the clinical picture of congenital hemolytic anemia and episodes of hemoglobinuria leading to death in from three to five years. Paroxysms occur during sleep at night and not during sleep in the daytime. There are present: anemia, jaundice, a constant hemoglobinemia of varying degree, hemosiderinuria, and frequently reduced kidney function. A positive Ham acid hemolysis test is diagnostic of the disease.

Paralytic hemoglobinuria (*myoglobin*). This disease is characterized by red urine and the rapid development of paralysis of muscles, with collapse. It occurs chiefly in horses. Only seven or eight cases have been reported in man. It usually occurs in well-fed horses who do not work for a period of two to three days. On resumption of work, the stored glycogen frees lactic acid damaging the muscles and liberating myoglobin which is excreted by the kidney. This is recognized or identified by spectroscopic examination. Myoglobin is readily excreted from the kidneys because of its lower molecular weight (myoglobin 16,500, hemoglobin 68,000) and the plasma usually is clear.

March hemoglobinuria. This has been adequately described in the first part of this paper. However, the fact that there is no positive diagnostic test known should be emphasized. The diagnosis is made by exclusion of other forms of hemoglobinuria.

EXOGENOUS

Favism. This disease is due either to the ingestion or inhalation of the poisonous principle of the plant vicia fava, commonly known as the broad or horse bean. This plant is found chiefly in the Mediterranean area and especially in Sardinia. It appears less frequently in Sicily, Italy, the Greek Islands, and North Africa. Symptoms develop within a few minutes after inhalation and a few hours after ingestion of the fava bean. General malaise, headaches, nausea, and dizziness appear early, followed by chilling, lumbar pains, fever, and later by hemoglobinuria and jaundice. The jaundice is very intense and in severe cases death occurs in two or three days. It is nearly always fatal in children. In mild cases the jaundice and hemoglobinuria resolve in five or six days. The differential diagnosis of these five types of hemoglobinuria is shown in figure 2, *B*.

There is another large group of hemoglobinurias which does not fit into this classification. They must be kept in mind in making the differential diagnosis. This group which is probably the most common, comprises the types of hemoglobinuria due to intravascular hemolysis from such causes as transfusion reactions, burns, the crush syndrome, and toxic conditions. The causes of toxic hemoglobinurias are many, i.e., following ingestion of sulfonamide, of quinine in fatal doses, after certain snake and spider bites, from the toxin of Clostridium welchii, and following inhalation of arsine or arsenuretted hydrogen gas.

This case fulfills the diagnostic criteria of march hemoglobinuria. It was produced by exertion in the upright position. Oxyhemoglobin in urine and plasma was spectroscopically proven; the Wassermann test, the Donath-Landsteiner reaction, and the Ham acid hemolysis reaction were negative. There was no history of exposure to fava beans and there were no symptoms such as jaundice, or chills.

SUMMARY

The sixty-first proven case of march hemoglobinuria is presented with the urine and plasma findings after exertion. A short review of the differential diagnosis of hemoglobinurias is given.

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UROGENITAL ASPECTS OF COCCIDIOIDOMYCOSIS: REVIEW OF THE LITERATURE AND REPORT OF TWO CASES

JAMES G. ROHN, JULIO C. DAVILA AND THOMAS E. GIBSON

From the Department of Urology of the Southern Pacific General Hospital, San Francisco, Calif.

The unexpected occurrence of coccidioidal granuloma in the epididymis of a patient in the Southern Pacific General Hospital prompted the investigation which led to this paper. The scarcity of material available and the lack of emphasis placed by the existing literature on the urogenital aspects of this disease limit this survey to pointing out the occurrence and to attempting an evaluation of the importance of this form of coccidioidomycosis.

It may be well to mention certain general features of the disease. The causative agent, Coccidioides immitis, exists in the soil of the arid regions of the southwestern United States and northwestern Mexico, as well as in certain regions of South America. In its saprophytic phase its hyphae develop arthrospores and chlamydospores, which are very easily dust-borne. It is in this form that infection is acquired, usually by inhalation, and rarely through open cutaneous wounds or abrasions. Once in the human organism, the chlamydospores become the doubly refractile spherules which are diagnostic of the disease. These spherules reproduce by endosporulation, within the tissues. The disease is not communicable in the parasitic phase.

The prevalence of the disease has been demonstrated by mass skin-testing programs which reveal that practically all individuals living in endemic areas contract the infection at one time or another. Sixty per cent of these remain asymptomatic; in the rest, the disease ranges from a mild upper respiratory form, through severe pulmonary involvement, disseminated, and finally progressively disseminated states. The usual process is mild, involving only lung and mediastinal lymph nodes.

Typically, the primary infections heal completely, although residual pulmonary lesions, and even cavities, may persist. In approximately ¼ per cent of all infections in white males and three per cent of Negro males extrapulmonary foci may develop. Filipinos are even more susceptible to dissemination. Noncontiguous involvement may include any tissue or organ of the body. Spread is common to bone, lymph nodes, spleen, meninges, kidney, skin, adrenals, and liver. In approximately one-half of the disseminative infections, progression leads to death. However, except when meninges are involved, even very advanced cases may result in complete recovery. If a patient does recover he remains immune to exogenous re-infection.*

The characteristic pathological lesion is a typical infectious granuloma of varying size and developmental stage in any given tissue. It consists of a grouping of epithelioid cells, scattered giant cells, and often, central caseation. For

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* Personal communication from Dr. C. E. Smith.

Read at annual meeting, Western Section, American Urological Association, Yosemite Valley, Calif., May 9, 1950.

this reason it is frequently misdiagnosed as tuberculosis. However, the presence of the doubly refractile spherules makes the diagnosis obvious. These spherules are frequently found in smears of secretions from involved organs, as well as in tissue preparations.

The material for this paper was obtained from three sources: 1) one case seen by us in the urology clinic of the Southern Pacific General Hospital, and one case seen by Dr. C. S. Harrod in the clinics of the Stanford University Medical School; 2) case records from the Southern Pacific General Hospital; and 3) review of the pertinent literature.

SUMMARY OF TWO CASES

Case 1. A 40 year old Negro was admitted to the Southern Pacific General Hospital on October 15, 1949, complaining of swelling of the left scrotum since 1943.

In 1943, shortly after a febrile illness characterized by cough, expectoration, and prostration, bilateral swelling of the scrotum developed, accompanied by pain and fever, and lasting about six weeks. The right side subsided completely but swelling of the left scrotal contents persisted until the time of this admission. It was somewhat painful and uncomfortable. Aside from those mentioned above, no other urogenital symptoms were present in the course of these developments.

The patient was born near Houston, Texas, where he lived until 1946, employed as a railroad laborer. Since then he had remained in or about Sacramento, California. He reported that his past health had been robust except for two episodes of febrile illness; the second episode, which was diagnosed as malaria in 1943, has been mentioned previously. His genito-urinary past history was otherwise entirely negative, except for lues and gonorrhea in 1938, for which he received treatment.

The significant physical findings were limited to the left scrotal contents: a firm, nodular, enlarged epididymis, and a slightly enlarged, smooth, rubbery testicle. There was no tenderness to pressure or palpation. The mass did not transilluminate. On rectal examination, the prostate was found to be normal, and the seminal vesicles were not palpable. The remainder of the urogenital examination was not remarkable.

The complete blood count, urinalysis, Kolmer and Kahn tests were all within normal limits. Excretory urograms and roentgenograms of the chest were not significant.

At this time, the clinical impression was that of tuberculous epididymitis and exploration of the scrotum was recommended with the possibility of epididymectomy in mind. This was done on October 24, 1949. The epididymis was found to be enlarged, very firm, nodular, and firmly adherent to the testicle and cord. The gross appearance resembled a tuberculous epididymitis. In view of the normal appearance of the testicle, only the epididymis was excised, despite the difficulty in dissection. The pathological report stated: "This epididymis contains many tubercle-like lesions in which are rather frequent spherules of Coccidioides immitis (figs. 1 and 2). No tubercle bacilli are found."

On the third postoperative day headache and stiffness of the neck developed. The neurological examination and cerebrospinal fluid analysis were negative. The remaining course was uneventful, and by the fifteenth postoperative day the wound was completely healed.

In view of the diagnosis, certain studies were performed: On October 28, 1949, tuberculin skin test (1:1000) was negative after 48 hours; the coccidioidin skin test (1:1000) resulted in an indurated wheal measuring 2 by 3 by 0.3 cm. after 48 hours. On November 11, 1949, smears of prostatic secretions were negative for coccidioides. The patient was discharged on that date.

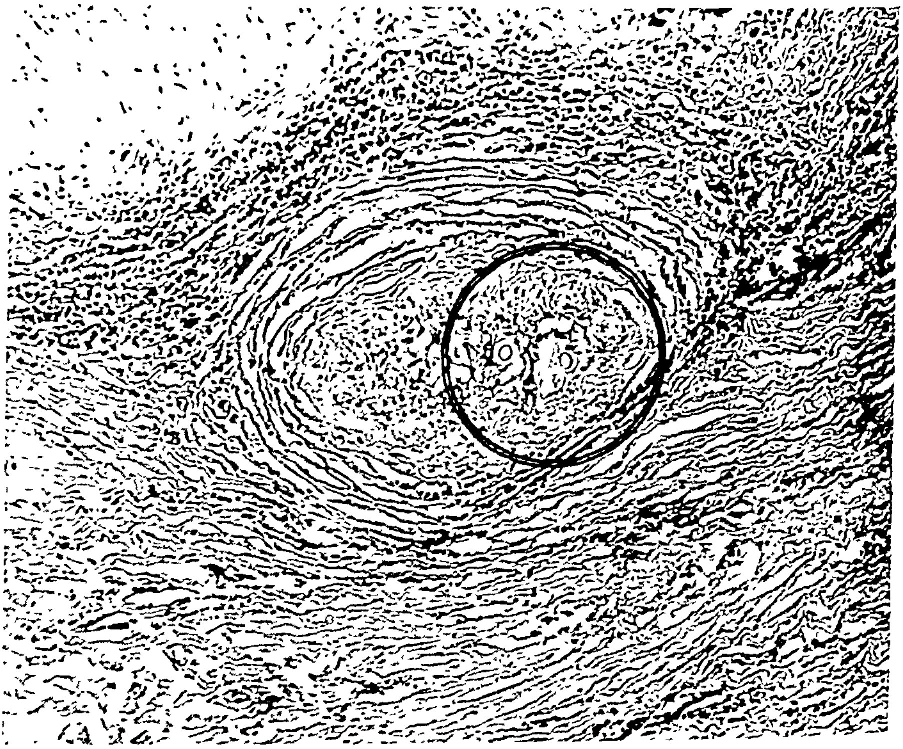

Fig. 1. Case 1. Low power magnification of section of epididymis showing conformation of coccidioidal lesion. Note dense area of fibrosis around tubercle. Tubules are found just outside this scarred region, but are not within this particular field.

One month later, when he returned for follow-up examination, blood taken for a complement fixation test was reported as 4 plus in a 1:2 dilution, but negative in all higher dilutions. The precipitin test was entirely negative. The report concluded: "Complement fixation is positive in a reassuringly low titre. While the lesion is disseminative, the outlook seems very favorable."

Case 2. A 38 year old Filipino was first seen in the bone and joint clinic of Stanford University Hospitals on November 27, 1946, where he appeared complaining of pain in both wrists and elbows of 3 years' duration. These joints, on aspiration, yielded a yellow, purulent material. The puncture sites drained for several months. On the basis of preoperative diagnosis of tuberculous arthritis, arthrodesis of the right wrist was performed in December 1946. A specimen of synovial membrane revealed coccidioidomycosis.

The patient was first seen in the urology clinic of that institution on February 5, 1947, at which time he complained of a "lump" in the right scrotum which had been present, gradually enlarging, nontender and nonpainful, over a period of 4 or 5 months.

The patient had been a farm worker from 1930 to 1942. He was in the San Joaquin Valley for a few months in 1936, and in Arizona prior to 1940. Until 1942 he was in the vicinity of Phoenix, Arizona, working in lettuce and cotton. In the fall of 1942, he had a severe "cold," and 2 months later his left elbow became swollen and drained.

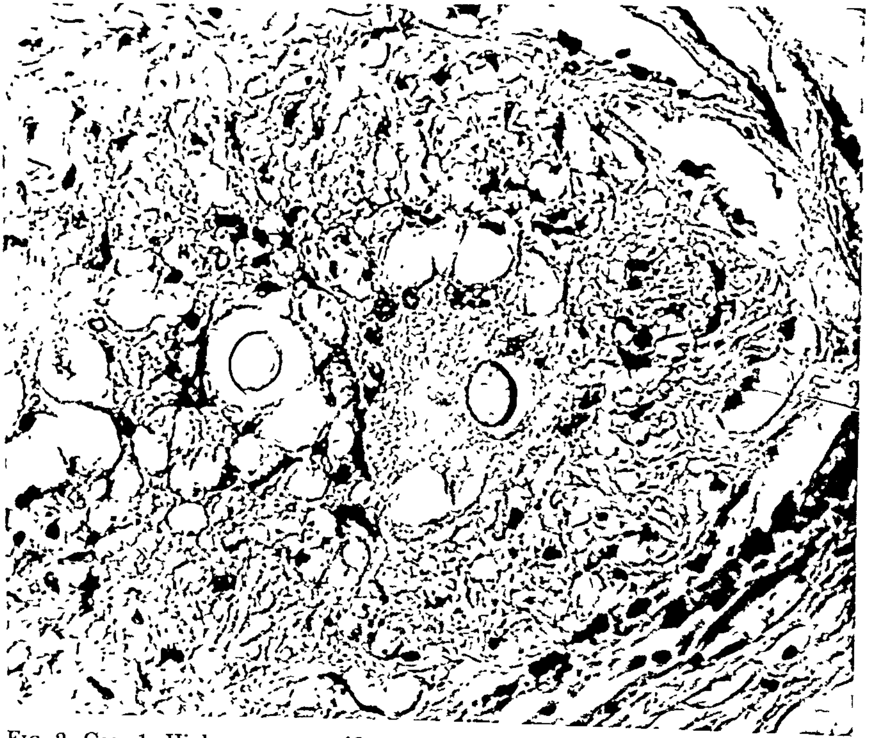

FIG 2. Case 1. High power magnification of area shown in inset in figure 1. Two coccidioidal spherules clearly demonstrated. One on right is within giant cell.

The physical examination of the urogenital system revealed only enlargement, nodularity and induration of the lower pole of the right epididymis. Involvement of the right testicle was questionable. The rectal examination revealed an induration of the right seminal vesicle. The kidney regions, the prostate, the left seminal vesicle, and the left scrotal contents and right vas were not remarkable.

Excretory urograms revealed only slight blunting of the right upper calyx.

On January 2, 1947, coccidioidin skin test was reported questionable in 1:10 and 1:100 concentrations. Histoplasmin was negative in 1:100 concentration.

On January 14, 1947, tuberculin skin test in 1:100 concentration was negative. Urinalysis, blood count, and Wassermann were negative. His coccidioidal complement fixation test was positive through a dilution of 1:128, characteristic of progressive dissemination.

On February 7, 1947, a right orchiectomy and left partial vasectomy were done. The upper and lower poles of the epididymis were enlarged. The upper pole was nodular. Epididymectomy was begun but in view of testicular invasion, orchiectomy was necessary (fig. 3). The postoperative course was uneventful. The patient was last seen on October 17, 1949, at which time he had no further urogenital symptoms. However, the process in the elbows was worse.

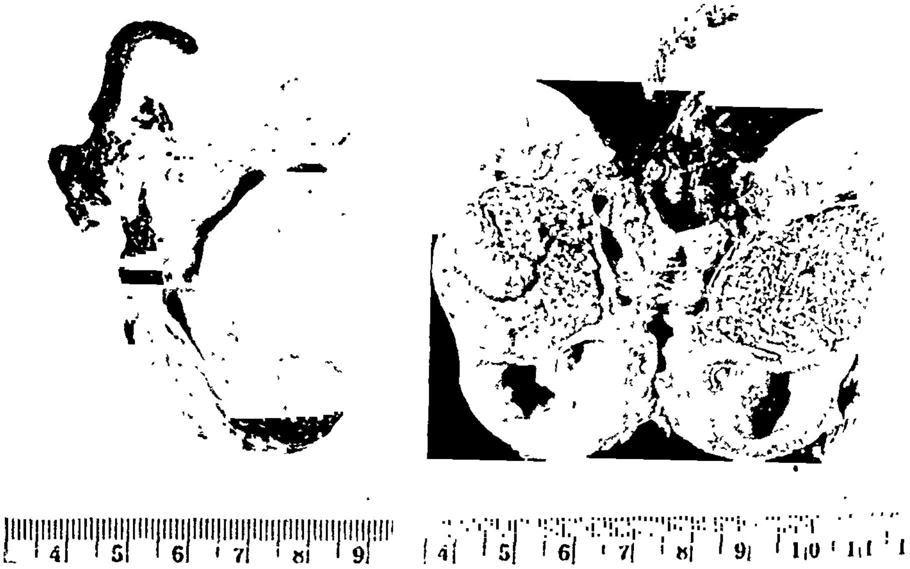

Fig. 3. Case 2. Showing uncut gross specimen, then view of same specimen on sagittal section. Note nodularity and enlargement of upper pole of epididymis. Testicular tissue is atrophic but free of infection. (Courtesy of Dr. C. S. Harrod.)

The report of the histological examination of the surgical specimen stated: "The epididymis is composed of numerous tubercles in a mass of moderately loose fibrous tissue with many lymphocytes, and plasma cells. There are occasional small abscesses filled with neutrophiles and granular debris. The tubercles consist of prominent centrally located Langhans type giant cells surrounded by epithelioid cells. Throughout the tissue, but predominating in the tubercles, are round to oval spherules measuring 20 to 80 micra in diameter, possessing thick walls, and showing no budding. A section of adjacent testis shows no involvement. However, the tubules are almost devoid of spermatogenic elements, and primarily contain vacuolated Sertoli cells. Diagnosis: Coccidioidomycosis of the epididymis, and atrophy of the testicle."*

* Acknowledgment is made to Dr. C. S. Harrod for these data; and to Dr. H. M. Weyrauch and Stanford University for permission to include the information in our report.

COMMENT

With regard to the first case it is of interest to note that the disease was, in all likelihood, contracted during the patient's residence in Houston, Texas. This city is outside the known endemic zones. The patient probably traveled through nearby endemic areas, or else was infected by some object contaminated by passage through such an area. This case, furthermore, exemplifies that of a solitary lesion which, once excised, appears to be cured. Proof of this cure will necessitate following his course over a much longer period of time.

In contrast to the first case, the second shows more extensive active lesions, and here the good result of extirpation is counterbalanced by the progression of the other disseminated lesions which implies a poor prognosis.

It must be pointed out that both of these cases are nonwhite, belonging to the two racial groups most likely to undergo serious dissemination.

SUMMARY OF CASES FROM SOUTHERN PACIFIC HOSPITAL RECORDS

A total of 47 cases of coccidioidomycosis, about 33 per cent of which were in the disseminative phase, have been seen at this hospital since 1929. Five of these have resulted fatally and 4 have come to autopsy. Only in one of these 4 cases were urogenital lesions encountered. The records showed that there was a single 2 mm. lesion in the right kidney parenchyma. This case was reported by Cummins, Smith and Halliday in 1929 in one of the earlier papers published on the disease. At no time was there clinical evidence of the existence of this lesion. The remaining 42 cases showed absolutely nothing which might be interpreted as proof of urogenital coccidioidal infection.

SURVEY OF THE LITERATURE

We have found accurate analysis of the incidence of this disease in the urogenital tract very difficult and necessarily inexact. With the exception of the case of McDougall and Kleinman of prostatitis, of our foregoing 2 cases; and of the 2 cases, also of epididymitis, in the course of publication, reported by Weyrauch, Norman and Bassett, all instances of genito-urinary infection which were mentioned in the literature were the result of autopsy findings. In a total of 214 autopsies reported by various authors, there were 57 instances of renal involvement, or 26.6 per cent; there were 4 instances of prostatic involvement, or 1.8 per cent; there were 2 instances of involvement of the epididymis, or 0.9 per cent; there was only 1 instance of involvement of seminal vesicles and testes, representing 0.4 per cent. Clinically manifested urogenital coccidioidomycosis has been reported previously in only 1 case, that published by McDougall and Kleinman in 1943, from which the following is taken: "A 52 year old white male . . . complaining of hematuria, tenderness of the knee and shoulder, cough, expectoration, and night sweats . . . examination showed hazy urine, shreds and a few white and red cells in both glasses. The prostate was enlarged about two plus and irregularly indurated. The prostatic fluid was purulent and somewhat blood-tinged . . . treatment with sulfa and massage was followed by softening of the gland . . . it was decided that an abscess was present and 10 cc of grayish-green pus was aspirated through the perineum . . . coccidioides immitis was found. Cystoscopic examination, cultures from both kidneys and retrograde pyelograms were negative." In this case the dissemination became progressive and ended fatally. Unfortunately no autopsy was performed.

DISCUSSION AND CONCLUSIONS

Despite the fact that not enough cases have been analyzed from a urological standpoint, a few conclusions of clinical value to the urologist can be drawn. Knowing the mode of infection, it is apparent that urogenital involvement is a secondary manifestation of the disease, occurring only in cases in which there is dissemination. In the vast majority of cases, urological manifestations of clinical significance are absent, even though there may be urogenital involvement. We know that coccidioidomycosis mimics tuberculosis in almost all respects with the notable exception of kidney invasion. Kidney lesions are found but it seems that these seldom progress to the point of becoming clinically significant. Rare instances of overwhelming dissemination are mentioned, in which there is such involvement of the urinary tract, even including the bladder, that the organism has been recovered from the urine. However, involvement of the renal pelvis, ureter or bladder is extremely unusual.

In the light of our findings, renal infection with coccidioides is of little importance to the urologist. On the other hand, genital involvement seems worthy of recognition.

Any case of isolated coccidioidal infection must, of course, be thoroughly investigated and evaluated in terms of extent of dissemination. Prognosis depends upon this evaluation.

No attempt is made here to evaluate treatment of this disease, but it should be mentioned that currently no satisfactory medical treatment has been developed. If an isolated lesion amenable to surgical removal occurs, excision may be of value.

SUMMARY

Two cases of coccidioidal epididymitis are reported. In one there was a single isolated residual focus in the epididymis, whereas, in the other there were widespread manifestations of dissemination as well.

In 47 cases of coccidioidomycosis from the records of the Southern Pacific General Hospital there was not a single instance (except case 1 of our report) with clinical urological manifestations.

The incidence of urogenital lesions in 214 autopsies is analyzed.

Coccidoidomycosis of the urinary tract is of little importance to the urologist.

Coccidioidal granuloma is an important entity in the differential diagnosis of genital granulomas.

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REFERENCES

Ashburn, L. L. and Emmons, C. W.: Arch. Path., 39: 3–8, 1945.
Burks, J. W. Jr. and Thompson, P. E.: South. Med. J., 39: 613–620, 1946.

Butt, E. M. and Hoffman, A. M.: Am. J. Path., 21: 485–505, 1945.
Cheney, G. and Denenholz, E. T.: Mil. Surg., 96: 148–156, 1945.
Clark, D. and Gilmore, J. H.: Ann. Int. Med., 24: 40–59, 1946.
Cohen, R. and Burnip, R.: Calif. Med., 72: 31–33, 1950.
Cummins, W. T., Smith, J. K. and Halliday, C. H.: J. A. M. A., 93: 1046–1049, 1929.
Dickson, E. C., and Gifford, M. A.: Arch. Int. Med., 62: 853–871, 1938.
Evans, N. and Ball, H. A.: J. A. M. A., 93: 1881–1885, 1929.
Forbus, W. D. and Bestebreurtje, A. M.: Mil. Surg., 99: 653–719, 1946.
Goldman, M. J. and Movitt E.: Calif. Med., 69: 456, 1948.
Goldstein, D. M. and McDonald, J. B.: J. A. M. A., 124: 557–561, 1944.
Harrod, C. S.: Personal communication.
Helper, M. and Watts, F. B.: Mil. Surg., 96: 524–527, 1945.
Kunstadter, R. H. and Pendergrass, R. C.: J. A. M. A., 127: 624–627, 1945.
Maple, C. D.: Ann. Int. Med., 23: 240–249, 1945.
McDougall, T. G. and Kleinman, A. H.: Jr. Urol., 49: 472–477, 1943.
Ophuls, W.: J. A. M. A., 45: 1291–1299, 1905.
Quill, L. M. and Burch, J. C.: Ann. Surg., 120: 670–679, 1944.
Riesman, D. and Ahlfeldt, F. E.: Am. J. Med. Sc., 174: 151–167, 1927.
Smith, C. E.: Personal communication.
Smith, C. E., Beard, R. R., Whiting, E. G. and Rosenberger, H. G.: Am. J. Pub. Health, 26: 1394–1402, 1946.
Snyder, B. L. and Rogers, G. K.: Ariz. Med., 5: 33–37, 1948.
Weyrauch, H. M., Norman, F. W. and Bassett, J. B.: In press, Calif. Med.
Willit, F. M. and Weiss, A.: Ann. Int. Med., 23: 349–375, 1945.

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EFFECT OF COMBINED THERAPY ON EMERGENCE OF DRUG RESISTANT BACTERIA IN URINARY TRACT INFECTIONS: OBSERVATIONS ON ORIGIN OF RESISTANT STRAINS

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The development of resistance of bacteria to chemotherapeutic and antibiotic agents has been a limiting factor in therapy.[1] The problem of the development of resistance to streptomycin had been a particularly serious one. It was found in vitro that such resistance could be inhibited by the combined use of streptomycin, penicillin and sulfadiazine.[2] Therapeutically, the overall effect of two or more antibacterial agents has frequently been found superior to that obtained with one drug[3] and some clinical studies have been carried out indicating that this therapeutic effect was correlated with the inhibition of drug resistance by combined therapy.[4]

Development of resistance has been a common finding in the treatment of urinary tract infections with streptomycin.[5] In the present study we were concerned with 1) the effectiveness of combined streptomycin, penicillin and sul-

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The streptomycin for the patients was supplied by E. R. Squibb and Sons, Inc., and by Merck and Co., Inc.

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[1] Buggs, C. W., Bronstein, B., Hershfeld, J. W. and Pilling, M. A.: J. A. M. A., 130: 64, 1946.
Finland, M., Murray, R., Harris, H. W., Kilham, L., and Meads, M.: J. A. M. A., 132: 16, 1946.
Youmans, G. P., Williston, E. H., Feldman, W. H. and Hinshaw, H. C.: Proc. Staff Meet. Mayo Clin., 21: 126, 1946.
Alexander, H. E., Leidy, G., Rake, G. and Donovick, R.: J. A. M. A., 132: 434, 1946.
Hall, W. H. and Spink, W. W.: Proc. Soc. Exper. Biol. & Med., 64: 403, 1947.

[2] Klein, M. and Kimmelman, L. J.: J. Bact., 54: 363, 1947.
Pulaski, E. J. and Baker, H. J.: J. Lab. & Clin. Med., 34: 186, 1949.

[3] Dowling, H. F., Hussey, H. H., Hirsh, H. L. and Wilhelm, F.: Ann. Int. Med., 25: 950, 1946.
Eisele, C. W. and MacCullough, N. B.: J. A. M. A., 135: 1053, 1947.
MacLean, J. T. and Smith, F.: Canad. M. A. J., 57: 131, 1947.
Lincoln, E. M., Kirmse, T. W. and DeVito, E.: J. A. M. A., 136: 593, 1948.
Kolmer, J. A.: Am. J. M. Sc., 215: 136, 1948.
Thatcher, F. S. and MacLean, J. T.: J. Urol., 57: 902, 1947.

[4a] Cocchi, E. and Pasquinucci, G.: Quoted in Pfuetze, K. and Myle, M.: J. A. M. A., 139: 634, 1949.

[b] Spink, W. W., Hall, W. H., Shaffer, J. and Braude, A. I.: J. A. M. A., 139: 352, 1949.

[c] Delaude, A., Karlson, A. G., Carr, D. T., Feldman, W. H. and Pfeutze, K. H.: Proc. Staff Meet. Mayo Clin., 24: 342, 1949.

[d] Karlson, A. G., Pfeutze, K. H., Carr, D. T., Feldman, W. H. and Hinshaw, H. C.: Proc. Staff Meet. Mayo Clin., 24: 85, 1949.

[5] Bondi, A., Ottenberg, D., Dietz, C. C. and Brown, C. L.: J. A. M. A., 132: 634, 1946.
Adcock, J. D. and Plumb, R. T.: J. A. M. A., 133: 579, 1947.
Harrell, G. T., Herndon, E. G., Gillikin, C. M. and Aikawa, J. K.: J. Clin. Investigation, 26: 577, 1947.

fonamide in inhibiting the development of resistant strains during the treatment of urinary infections, and 2) the origin of the resistant strains in the urinary tract.

MATERIALS AND METHODS

Cases and drug dosages.—A total of 37 cases from the urological services of the Hospital of the University of Pennsylvania and the Philadelphia General Hospital were studied. These included both uncomplicated urinary tract infections (cystitis, pyelonephritis, urethritis, etc.) and those complicated by additional pathological changes, such as calculi, strictures and obstructions.

All cases, unless otherwise indicated, had not received previous therapy with streptomycin, penicillin or sulfonamides as far as could be determined.

All patients (unless otherwise indicated) received the following daily dosage for a total of 7 days: streptomycin, 1.0 gm., intramuscularly; penicillin, 200,000 units, intramuscularly; sulfadiazine, 2.0 gm., orally. Alkali was not routinely given (except for patients numbers 11, 25, 27, 29 (tables 1 and 2) and the pH of the urines varied between 5.5 and 6.0. As will be indicated later, therapeutic response to combined therapy was excellent in all the simple urinary tract infections, in the presence or absence of alkali. When strains of Proteus were present in the urine, the pH varied between 8.0 and 8.2. Leukocyte counts, hemoglobin determinations, and microscopic urine analyses were followed during therapy and for 3 days to several months after therapy.

Urine specimens were obtained using aseptic precautions. In the male, preliminary sponging of the meatus or catheter tip with 70 per cent alcohol was carried out and samples were collected after urine had first rinsed the alcohol away. Samples were collected from the female by catheterization after perineal preparation. Urines were obtained before therapy and every 48 hours during the 7 days of therapy.

Laboratory procedures. Isolations: All specimens were centrifuged at high speed in an angle centrifuge for 20 minutes, and the supernate was discarded. If the specimen was taken during therapy, the sediment was washed in saline to remove any residual drugs. The washing procedure was found to eliminate the necessity of using drug-antagonists in the medium, since the addition of penicillinase, PABA and cysteine to the medium did not increase the amount of growth above that obtained from washed residues. Highly susceptible organisms were regularly isolated from washed specimens obtained from urines containing streptomycin, penicillin and sulfadiazine.

All specimens were 1) gram stained, 2) inoculated into beef extract broth, 3) streaked on brom thymol blue lactose agar or MacConkey's agar, and blood extract agar when gram positive cocci were observed in smear. All cultures were incubated aerobically at 37 C.

Since mixed coliform infections regularly occur in urinary tract infections,[4a, 5] at least 5 colonies of each coliform colony type were picked and identified. When the organisms were identified, they were placed on extract agar under sterile, heavy mineral oil for subsequent study of drug resistance.

Susceptibility tests: After completion of therapy, tests on all the organisms from each case were done simultaneously to determine the degree of susceptibility to each of the drugs. Dilutions of streptomycin (10 μ gm./ml. to 500 μ gm./ml.) and penicillin (0.1 unit/ml. to 5.0 units/ml.) were made in beef extract broth pH 7.2 and seeded with 0.1 ml. of 10^{-2} dilution of a 20–24 hour broth culture of the organism. A casein hydrolysate medium was used for determining

TABLE 1. *Bacteriological summary of urinary tract infections. Cases in which negative cultures were obtained after therapy*

CASE NO.	DIAGNOSIS	ORGANISMS ISOLATED BEFORE THERAPY	[a] IN VITRO SUSCEPTIBILITY TO			BACTERIOLOGY AFTER THERAPY
			SM.	P.	SD.	
1	Cystitis; pyelonephritis[b]	E. coli Staphylococcus aureus	S S	R S	S R	negative (Staphylococcus-resist. to SM. and SD.)[c]
2	Cystitis	E. coli	S	R	S	negative
3	Cystitis	E. coli	S	R	S	negative
4	Pyelonephritis (right)	Paracol. coliforme	S	R	S	negative[d]
5	Pyelonephritis	A. aerogenes	S	R	S	negative
6	Bilateral renal calculi	E. coli	S	R	S	negative
7	Renal (staghorn) calculi	Kl. pneumoniae	S	R	O	negative
9	Cystitis; pyuria	E. coli	S	R	S	negative
10	Acute right pyelonephritis	E. coli	S	R	S	negative
11*	Cystitis	Staphylococcus albus	S	R	S	negative
12	Acute cystitis (post-cystoscopy)	E. coli	R	R	R	negative
13	Epididymitis	Paracol. aerogenoides	S	R	S	negative
14	Cystitis and prostatitis	E. coli Paracol. coliforme	S S	R R	S S	negative
15	Acute pyelonephritis	E. coli	S	R	S	negative
16	Acute cystitis[b]	E. coli	S	R	S	negative[e]
17	Chronic pyelonephritis and glomerular nephritis	Alpha hemolytic streptococcus	S	S	O	negative[f]

* Received sodium bicarbonate 5.0 gm. every six hours in addition to the three agents.

[a] Susceptibility defined in METHODS AND MATERIALS: SM. denotes streptomycin; P., penicillin; and SD., sulfadiazine. O = no growth in medium (casein hydrolysate); S = susceptible; and R = resistant.

[b] Previous therapy given: case 16 received penicillin and case 1, penicillin and sulfadiazine.

[c] Probable contaminant; only few scattered colonies.

[d] *Paracolobactrum coliforme* persisted for more than four days, still susceptible to streptomycin and sulfadiazine, and eventually disappeared.

[e] *E. coli* recovered one month later, still susceptible, and retreated with permanent success.

[f] Streptomycin-susceptible alpha hemolytic streptococcus isolated two weeks later.

Note: Case 8 was omitted because no organisms were isolated before or after therapy.

TABLE 2. *Bacteriological summary of urinary tract infections. Cases in which resistant organisms were found after therapy*

CASE NO.	DIAGNOSIS	ORGANISMS ISOLATED BEFORE THERAPY	^{a} IN VITRO SUSCEPTIBILITY TO			ORGANISMS ISOLATED AFTER THERAPY	^{a} IN VITRO SUSCEPTIBILITY TO		
			SM.	P.	SD.		SM.	P.	SD.
18	Pyelonephritis	E. coli	S	R	S	A. aerogenes	R	R	R
19	Pyelitis; prostatitis	Proteus vulgaris	S	R	R	Proteus rettgeri	R	R	R
		Pseud. aeruginosa	R	R	R	Pseud. aeruginosa	R	R	R
						A. aerogenes	R	R	R
20	Chronic prostatitis and cystitis	Non-hemolytic Streptococcus	S	R	O^b	Non-hemolytic Streptococcus	R	R	R
		A. fecalis	R	R	R	Staph. aureus	R	R	R
21	Benign prostatic hypertrophy; cystitits	Staph. aureus	S	S	S	Staph. aureus	R	R	R
22	Benign prostatic hypertrophy	E. coli	S	R	S	A. aerogenes	R	R	R
23	Chronic pyelonephritis	A. aerogenes	S	R	S	A. aerogenes	R	R	R
24	Calculus at ureteropelvic junction	E. coli	S	R	S	A. aerogenes	R	R	R
		Paracol. coliforme	S	R	S	Proteus mirabilis	R	R	R
25*	Bilateral renal calculi	Proteus mirabilis	R	R	R	Proteus mirabilis	R	R	R
		Pseud. aeruginosa	R	R	R				
26	Hydronephrosis (congenital band)	Proteus rettgeri	R	R	R	Proteus rettgeri	R	R	R
		A. fecalis	R	R	R	Paracol. coliforme	R	R	R
27*	Calculus	Proteus morgani	S	R	R	A. aerogenes	R	R	R
						Proteus mirabilis	R	R	R
28	Renal carbuncle; pyelonephritis	Anaerogenic Paracol. species	S	S	O^c	Anaerogenic Paracol. species	R	R	O^c
29*	Renal and ureteral calculi	A. aerogenes	S	R	S	A. aerogenes	R	R	R
		A. fecalis	R	S	S	Proteus rettgeri	R	R	R
30	Bilateral calculi	Proteus mirabilis	S	S	S	Proteus morgani^d	S	R	S
31	Neurogenic bladder; carcinoma; cystitis; calculus	E. coli	S	R	S	A. aerogenes	R	R	R
		A. aerogenes	S	R	S	Proteus rettgeri	R	R	R
						Pseud. aeruginosa	R	R	R
32	Ureteral stricture; pyelonephritis	E. coli	S	R	S	Staph. albus	R	R	R
33	Hemorrhagic cystitis; diverticulum	Staph. aureus	S	R	R	Pseud. aeruginosa	R	R	R
						A. aerogenes	R	R	R

TABLE 2—*Continued*

CASE NO.	DIAGNOSIS	ORGANISMS ISOLATED BEFORE THERAPY	[a] IN VITRO SUSCEPTIBILITY TO			ORGANISMS ISOLATED AFTER THERAPY	[a] IN VITRO SUSCEPTIBILITY TO		
			SM.	P.	SD.		SM.	P.	SD.
34	Benign prostatic hypertorphy; multiple myeloma	A. aerogenes Paracol. aerogenoides	R R	R R	R R	A. aerogenes	R	R	R
35	Benign prostatic hypertrophy	Staph. aureus	S	R	S	A. aerogenes	R	R	R
36	Post-herniorrhaphy cystitis and/or prostatitis	A. aerogenes	R	R	R	A. aerogenes	R	R	R
37	Acute pyelonephritis; urethral stricture	Proteus mirabilis	R	R	R	Proteus mirabilis A. aerogenes Coliform-intermediate Proteus rettgeri	R R R R	R R R R	R R R 0[c]
38	Benign prostatic hypertrophy; surgery	E. coli	S	R	S	A. aerogenes	R	R	R

* Received sodium bicarbonate in addition to the other drugs.

[a] Susceptibility defined in METHODS AND MATERIALS: SM. denotes streptomycin; P., penicillin; and SD., sulfadiazine. S = susceptible and R = resistant.

[b] Previous therapy given: case 27 received penicillin; case 36, penicillin and sulfadiazine; and case 34, a full course of streptomycin, penicillin and sulfadiazine, 3 weeks before.

[c] Could not be grown in casein hydrolysate medium with special vitamin additions.

[d] One colony only on isolation plate.

Note: Cases 19, 31, 33, and 37 were from the Philadelphia General Hospital through the courtesy of Dr. Earl W. Clawater. These were given a triple sulfonamide preparation (Lilly) consisting of sulfapyrazine, sulfamerazine and sulfadiazine (0.167 gm. of each per tablet).

sulfonamide susceptibility of the organisms.[6] All tubes were seeded with 0.1 ml. of a 10^{-4} dilution of a 20–24 hour broth culture.

The lowest concentration of drugs showing complete inhibition of growth after 24 hours at 37 C was taken as the inhibitory concentration. Resistant strains are arbitrarily defined in the present study as those growing in at least 25.0 μ/ml. streptomycin, 1.0 unit/ml. penicillin and 1:25,000 sulfadiazine.

RESULTS

Bacteriological findings. Comparative success in simple and complicated infections:—The results obtained in the 37 cases are shown in tables 1 and 2. In table 1 are listed the cases in which no organisms were isolated after 7 days of combined therapy. It may be noted that of 16 cases, 14 were uncomplicated urinary tract infections. The organisms generally found before therapy were gram-negative bacilli, usually susceptible to streptomycin and sulfadiazine and resistant to penicillin. Gram-positive cocci (staphylococci and enterococci) were found only occasionally in the urines.

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[6] Strauss, E., Dingle, J. H. and Finland, M.: J. Immunol., 42: 331, 1941.

Table 2 lists the cases of bacteriological failure. Nineteen of the 21 cases were complicated by the presence of calculi, hypertrophy, strictures, etc. With one exception (case 30) in all of the 21 cases, bacteria present after 7 days' therapy were found resistant to all three drugs.

It is quite evident, therefore, that in the presence of factors complicating the infectious process, combined therapy did not permanently eliminate bacteria from the urinary tract. Although success was obtained in eliminating bacteria in 15 of the 16 cases of simple urinary tract infections (table 1), the series is too small to determine whether or not combined therapy is superior to the results obtained by the use of one drug. In approximately 55 per cent of all these cases the initial flora was eliminated by the third day. This is an indication of the effectiveness of combined therapy in eliminating the initial flora, although not a measure of the eventual bacteriological outcome.

TABLE 3. *Incidence of urinary strains and susceptibility to streptomycin. Isolations before and after combined therapy*

ORGANISM	BEFORE THERAPY			AFTER THERAPY		
	Number of Strains			Number of strains		
	Susceptible	Resistant	Total	Susceptible	Resistant[a]	Total
Escherichia coli	15	1	16	1	0	1[b]
Aerobacter aerogenes	4	2[c]	6	0	14	14
Proteus species	3	3	6	1	9	10
Pseudomonas aeruginosa	0	2	2	0	3	3
Paracolobactrum species	5	1	6	0	2	2
Staphylococcus species	5	0	5	0	3[d]	3
Alkaligenes fecalis	0	3	3	x	x	0
Streptococcus species	2	0	2	0	1	1
Klebsiella pneumoniae	1	0	1	x	x	0
Coliform-intermediate	0	0	0	0	1	1

x = No strains encountered at all after therapy.

[a] All resistant to penicillin, streptomycin, and sulfadiazine excepting one strain of Proteus susceptible to sulfadiazine and one strain of staphylococcus susceptible to penicillin.

[b] One susceptible and apparently identical strain isolated 2 weeks later, also.

[c] One case found subsequently to have had one course of combined therapy before this course.

[d] Status of one or more strains as contaminants very likely.

Resistant urinary strains.—The incidence of the development of resistant strains is shown in tables 1 and 2 and summarized in table 3. It is quite clear that the use of combined therapy did not consistently prevent the ultimate appearance of resistant bacteria. It should be noted, however, that the originally susceptible strains were usually eliminated and the resistant strains emerging represented new species, resistant to all three drugs.

In 14 of 21 cases in table 2, the resistant strains isolated after therapy were

TABLE 4. *Comparison of urinary and fecal flora before and after combined therapy*

CASE NO.	DIAGNOSIS	BEFORE THERAPY								AFTER THERAPY							
		Urine	[a]Susceptibility To			Feces*	[a]Susceptibility To			Urine	[a]Susceptibility To			Feces*	[a]Susceptibility To		
			SM.	P.	SD.		SM.	P.	SD.		SM.	P.	SD.		SM.	P.	SD.
23	Chronic pyelonephritis; previous nephrectomy	A. aerogenes[c]	S	R	S	A. aerogenes	S	R	S	A. aerogenes[c]	R	R	R	A. aerogenes[c]	R	R	R
						E. coli	S	R	S								
						Coliform-intermediate	S	R	S								
24	Calculus and infection at uretero-renal junction	E. coli	S	R	S	A. aerogenes	S	R	S	Proteus mirabilis	R	R	R	Proteus mirabilis	R	R	R
		Paracol. coliforme	S	R	S	Paracol. intermedium	S	R	S	A. aerogenes	R	R	R	A. aerogenes	R	R	R
						Coliform-intermediate	S	R	S								
25	Bilateral renal calculi; previous surgery; surgery now also before therapy	Proteus mirabilis	R	R	R	Proteus mirabilis	R	R	R	Proteus mirabilis	R	R	R	E. coli	S	R	R
		Pseud. aeruginosa	R	R	R	E. coli	S	R	S					Proteus mirabilis	R	R	R
														E. coli	R	R	S
36	Post-herniorrhaphy; cystitis and prostatitis	A. aerogenes	R	R	R	A. aerogenes	R	R	R	A. aerogenes	R	R	R	A. aerogenes	R	R	R
						Coliform-intermediate	R	R	S								
33	Hemorrhagic cystitis, diverticulum; surgery after therapy	Staph. aureus	S	R	R	E. coli	S	R	S	A. aerogenes	R	R	R	A. aerogenes	R	R	R
						A. aerogenes	S	R	S	Pseud. aeruginosa[d]	R	R	R	E. coli	S	R	R
						Coliform-intermediate	S	R	S					Paracol. intermedium	R	R	R
34	Benign prostatic hypertrophy, surgery, multiple myeloma[b]	A. aerogenes	R	R	R	Proteus vulgaris	S	R	S	A. aerogenes	R	R	R	A. aerogenes	R	R	R
		Paracol. aerogenoides	R	R	R	Paracol. aerogenoides	S	R	S					Proteus rettgeri	R	R	0

37	Urethral stricture, febrile pyelonephritis	Proteus mirabilis[e]	R	R	R	Proteus mirabilis	R	R	R	Proteus mirabilis	R	R	R	Proteus mirabilis	R	R	R
										A. aerogenes	R	R	R	Paracol. coliforme	S	R	S
										Coliform-intermediate	R	R	R				
										Proteus rettgeri	R	R	0				

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[*] Since the great majority of strains isolated from the urines were gram-negative bacilli, the study of the feces was limited to the isolation of gram-negative bacilli.

[a] Susceptibility defined in METHODS AND MATERIALS: SM. denotes streptomycin; P., penicillin; and SD., sulfadiazine. S = susceptible; R = resistant; 0 = no growth.

[b] Previous therapy given: case 31 received a full course of streptomycin, penicillin and sulfadiazine, 3 weeks before.

[c] The initial A. aerogenes differs biochemically and serologically from the final A. aerogenes; the final urine and fecal strains of A. aerogenes are apparently identical, however.

[d] Isolated after 2 days of therapy but not present in final culture.

[e] Isolated from the blood; no urine received.

not recovered prior to therapy. This pattern of change in flora has previously been observed by others during treatment of urinary tract infections.[7]

E. coli, which was present initially in 16 of the cases (tables 1 and 2), was eventually eliminated in all cases and never emerged as a resistant strain (table 3). A. aerogenes on the other hand, though initially present in only 6 cases, was found in 14 cases to be resistant to all three drugs after therapy. This striking difference in the development of resistance of E. coli and A. aerogenes will be considered further in the relationship of the urinary to the fecal flora.

Proteus species and Pseudomonas aeruginosa were associated with the complicated cases. The species of Proteus often changed during the course of therapy, but when a strain was initially resistant, it remained as a final resistant strain. Resistance was observed in virtually all these strains after therapy. A Pseudomonas strain (case 19), although initially resistant, was not present at the end of therapy.

The alkali apparently was of no added help in the 3 complicated cases (table 2). The simple infections did well without alkali.

Correlation between fecal and urinary flora:—The presence and origin of resistant bacteria in the urine were of particular interest. It has been felt by many that the bacteria in the urine have their origins in the fecal flora.[8] Bacteriological study of the fecal flora is obviously a complex problem. It was believed, however, that study of the correlation between the fecal and urinary flora would be simpler in patients receiving combined therapy, since there would be 1) a marked reduction of the total number of organisms in the feces, and 2) the development of specific resistance to three drugs in the strains, would offer a method for correlating the flora of the urine and feces.

A total of 7 cases were studied in which an attempt was made to correlate the fecal and urinary flora. The experimental procedure was as follows: a pea-sized portion of feces was emulsified in 0.5 ml. of sterile water, and approximately 0.05 ml. of the suspension spread over media for isolation; the procedures for identification and susceptibility tests were as carried out in the study of the flora of the urinary tract. Since the smears and the isolations from the urines after therapy rarely revealed gram-positive cocci, no attempt was made to recover them from the feces.

The criteria for establishing a correlation between the flora of the colon and the urine are considered to be the following: 1) an organism found in the feces resistant to all three drugs should be present in the urine; 2) an organism found in the feces susceptible to any of the three drugs should not be present in the urine; 3) an organism found resistant in the urine should be present in the feces.

In cases 33, 34, 37 (table 4) the correlation between the fecal and urinary flora is at best suggestive; a resistant strain in the feces was not found in the urine, e.g., the Paracolobactrum strain in case 33. Also, resistant strains in the urine, e.g., case 37, A. aerogenes and Coliform-intermediate were not found in the feces. The results in these three cases may well indicate a lack of correlation between the fecal and urinary flora. It should be pointed out, however, that the failure to isolate bacteria, particularly from the feces, may not be due to their absence but to the technical difficulties inherent in fecal isolations. Further, in those cases in which bacteria were found in the urine and not in the feces, the results may also be interpreted as indicating sources of gram-negative bacilli other than directly from the feces (catheterization, cystoscopies, as well as open procedures).

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[7] Harris, H. W., Murray, R., Paine, T. F., Kilham, L. and Finland, M.: Am. J. Med., 2: 229, 1947.

Bandler, C. G., Roen, P. R. and Mulaire, V. J.: J. Urol., 59: 96, 1948.

[8] Redewill, F. H., Potter, J. E. and Garrison, H. A.: References in the J. A. M. A., 94: 688, 1930.

In cases 23, 24, 25, 36, the correlation between the flora of the urine and feces is complete; strains of resistant bacteria found in the urine were found in the feces. E. coli isolated in the feces of 24, 25, 33, and the Paracolobactrum organism in 37, were still susceptible to one of the chemotherapeutic agents and did not establish themselves in the urinary tract.

It is believed that these results do permit the conclusion that there is a definite correlation between the urine and fecal flora and that the feces probably represent a major source of resistant strains isolated from the urine after therapy.

Clinical findings.—Noticeable clinical improvement was found in almost every case within a day or two after therapy was instituted. Even in the cases complicated by calculi, intubations, etc., dramatic symptomatic improvement was often observed. Fever, symptoms, leukocyte counts, and urine white cells were usually reduced before 48 hours. These improvements were obtained in the face of very obvious resistant bacillurias.

Except for one patient (case 27), who received several courses, no toxicity ascribable to the use of this combined therapy was noted. This patient showed a transitory deafness and tinnitus, which may have been due to the streptomycin alone.

DISCUSSION

If the colon is the source of infection, as indicated in our study, then complete therapeutic success theoretically requires the permanent elimination of the fecal bacteria involved in complicated urinary tract infections. Since there is little reason to believe that any therapeutic agent or combination of agents can permanently sterilize the intestinal tract, one should not expect that chemotherapy alone would effect lasting cure in obstructive cases. This interpretation is quite consistent with the usual failure of any chemotherapeutic agents to eliminate bacteria permanently from complicated urinary tract infections.

It should follow, therefore, that in the presence of urinary tract infections the temporary elimination of bacteria in the colon should be reflected in their temporary disappearance from the urinary tract. This has been observed with sulfasuxidine[9a] and sulfathalidine[9b] where the action of the compounds is essentially limited to the flora of the colon. Experimental evidence that bacteria can pass the intact colon is found in a study of nephrectomized dogs, injected intraperitoneally with a dialyzing solution, in which transmural escape of coliform organisms occurred, unless sulfathalidine and oral streptomycin were given.[10]

[9a] Everett, H. S., Scott, R. B. and Steptoe, P. P.: Am. J. Obst. & Gynec., 49: 114, 1945.
[b] Everett, H. S., Vosberg, G. A. and Davis, J. M.: J. Urol., 59: 83, 1948.
[c] Bandler, C. G. and Roen, P. R.: Ann. Surg., 128: 80, 1948.

A striking difference was observed in our study between E. coli and A. aerogenes strains in their susceptibilities and development of resistance. In the 16 strains of E. coli isolated from the urine, none became resistant during therapy and all were successfully eliminated from the urine. In those cases in which the fecal flora was studied no strain of E. coli isolated during therapy was found to have become resistant to all three drugs in the feces. On the other hand, A. aerogenes frequently emerged in the urine and feces resistant to all three drugs. In another recent study,[11] when streptomycin alone was given orally or intramuscularly, the resistant fecal organisms recovered were most commonly E. coli.

It is interesting that virtually all of these cases responded well clinically, at least temporarily. Although we have no data concerning this phenomenon, it is possible that the original flora was more toxic than the immediately succeeding flora. It has been shown[12] that certain E. coli strains from peritoneal and urinary infections were more apt to cause toxic manifestations (mouse pathogenicity, hemolysis, skin necrosis) than E. coli strains from normal feces. This, of course, does not explain cases of clinical response where no change in flora took place. As long as the obstruction remained the possibility of reinfection with a toxic strain remained.

Resistant strains generally appeared 2–3 days after the beginning of therapy, and the resistance was usually very great; at least 50-fold increase in streptomycin resistance (growth in at least 500 μ/ml.); at least 100-fold increase in sulfadiazine resistance (growth in 1:1000 dilution). This high streptomycin resistance is very interesting in view of the low level of streptomycin in the feces expected after intramuscular administration.[13] Almost all of the gram-negative bacilli were initially susceptible to streptomycin and sulfadiazine and resistant to penicillin.

It has been observed in urinary tract infections that changes in flora occur during therapy.[7] We believe that the obvious interpretation is that susceptible bacteria are inhibited or destroyed and the resistant strains survive and multiply. We considered as an alternate possible interpretation of this phenomenon that an organism such as A. aerogenes which was often found following therapy might actually play a rôle in inhibiting the multiplication of those bacteria which had disappeared during therapy. However, in vitro tests showed no evidence of inhibition of these organisms by A. aerogenes. In addition to changes in flora we have noted that even in the few cases in which ostensibly there is no change in species, e.g., A. aerogenes constantly present in the urine (case 23),

[10] Schweinburg, H. B., Frank, F. A., Frank, E. D., Heimberg, F. and Fine, J.: Proc. Soc. Exper. Biol. & Med., 71: 150, 1949.

[11] Hamburger, M. and Berman, J.: J. Clin. Investigation, 28: 1042, 1949.

[12] Sjöstedt, S., quoted by Kaufmann, F.: J. Immunol., 57: 71, 1947.

[13] Zintel, H. A., Flippin, H. F., Nichols, A. C., Wiley, M. M. and Rhoads, J.: Am. J. M. Sc., 210: 421, 1945.

biochemical and serological studies revealed that a different strain of A. aerogenes had appeared.

Success in combined therapy has been reported in a number of infections, but there have been only a limited number of studies concerned with the inhibition of the development of drug resistance. In brucellosis, for example, a combination of streptomycin and sulfadiazine has led to an inhibition of drug resistance.[4b] Combined streptomycin and para-aminosalicylic acid have been effective against M. tuberculosis in vitro[4d] and in vivo,[15] and have prevented development of streptomycin resistance. The inhibition of the development of drug resistance has also been observed in tuberculosis with streptomycin and promin.[4a, d]

One may ask why resistant strains arise, in view of in vitro and in vivo evidence that combined therapy can inhibit the development of resistance. The colon is unique in that there are a far greater number of bacterial individuals than are ever present in any infection. It may therefore be possible that, following the elimination of the majority of susceptible strains from this enormous population, there may be present or there may emerge a few bacteria simultaneously resistant to two or more drugs,[14] thus providing a potential source of resistant urinary organisms.

It is felt, then, that in view of the effectiveness of combined therapy in inhibiting the development of resistance in vitro,—and in vivo as referred to above—that the failure to inhibit the development of resistance in the present work should not be considered representative for the reasons that have been discussed.

In the present study it was found that bacteria initially present as drug-sensitive strains in the urinary tract were generally eliminated during therapy and did not develop into resistant strains. These results may be interpreted as indicating that combined therapy inhibited development of drug resistance. The finding of new strains of resistant bacteria during or after treatment appears to represent, as we have indicated, a problem peculiar to urinary tract infections. It is felt, therefore, that although resistant strains do emerge during combined therapy, they do not originate as susceptible organisms in the urinary tract, but that they can be traced to the immense intestinal flora, in which similar resistant strains have been found.

Studies are now being carried out on fecal flora changes under streptomycin (and combined drugs) in vitro.

SUMMARY AND CONCLUSIONS

The therapeutic effects of combined streptomycin, penicillin and sulfadiazine were studied in 37 cases of urinary tract infection.

Following therapy, sterile urine cultures were obtained in 16 cases, 14 of which were uncomplicated urinary tract infections.

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[14] Dalton, H.: Nature, 162: 227, 1948.
Spaulding, E. H., Madajewski, D. S., Rowe, R. J. and Bacon, H. E.: J. Bact., 58: 279, 1949.

[15] Vennesland, K., Ebert, R. H. and Bloch, R. G.: Proc. Soc. Exper. Biol. & Med., 68: 250, 1948.
Graessle, O. E., and Pietrowski, J. J.: J. Bact., 57: 459, 1949.

Therapy was bacteriologically unsuccessful in 21 cases, 19 of which were characterized by some complication. In these 19 cases, bacteria resistant to all three drugs regularly emerged.

A study of resistant strains in the urine and feces of 7 patients strongly indicated that many of the resistant strains in the urine had their origins in the fecal flora of the patient.

Good clinical response was obtained in virtually all of the cases in spite of persistent bacillurias.

Patients under therapy showed no evidence of toxicity due to the combined use of the three drugs.

Efforts to remove the source of obstruction or complication must be made in order for combined therapy to be of any permanent value.

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USE OF SUMP DRAINAGE FOLLOWING OPERATIVE PROCEDURES IN LOWER PELVIS

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A frequent complication following urological operations in the true pelvis, such as retropubic prostatectomy and total cystectomy, has been a persistent suprapubic sinus. This, while not serious in most cases, has been distressing to both the patient and surgeon and has in many instances significantly lengthened the convalescent period. It is also our opinion that osteitis pubis *may* be caused by the occurrence of infection in an undrained collection of fluid in the retropubic space. This disabling condition, while not occurring in our series of retropubic prostatectomies has been reported in the literature with some frequency.

A sinus forms in the wound, usually at the site from which the rubber drain was removed. This discharges a serosanguineous material which in some cases becomes purulent. This sinus persists for a period of 2 to 6 weeks, and in the case of a total cystectomy has lasted as long as 3 months.

Sinuses that follow retropubic prostatectomy have repeatedly been proven to be true sinuses and not urinary fistulas as evidenced by the failure of orally administered methylene blue to appear on the dressings.

Modifications in technique have been tried including the use of different types of rubber drains, oxycel in the retropubic space, having the patient spend some part of each hour lying on his face, etc. None of these has proved satisfactory in reducing the incidence of a persistent suprapubic sinus. It has been found that the type of static drain used had little, if any effect, nor did it seem to matter when the drain was removed. Oxycel seemed to aggravate the condition and it has been discarded.

It is believed that the primary cause of this condition is the anatomical fact that the lower or true pelvis, which includes the space of Retzius, lies at a lower level than the inferior end of the abdominal incision and, therefore, it is physically impossible to drain this space adequately by the usual methods. In any pelvic operation there is an inevitable separation of tissue planes, and it is apparent, therefore, that there will be tissue reaction resulting in the formation of an inflammatory exudate. If this is of negligible amount it may be reabsorbed, but if of larger quantity it must escape and it does so by way of the suprapubic wound. It may remain sterile and frequently does so, but it is a rich culture medium and so is easily infected.

As this complication was of sufficient frequency to definitely increase the morbidity following an otherwise entirely satisfactory surgical procedure, it was decided to attempt better drainage of the retropubic space by suction and the use of a sump drain.

Read at meeting of Northeastern Section, American Urological Association, Bigwin Inn, Lake of Bays, Ontario, Canada, September 7, 1949.

Sump drainage is a well known surgical procedure, which does not need elaboration. Most of the commercial drains of this type are metal and their use in this position in close, if not actual, contact with the pubis was felt to be hazardous.

A simple, inexpensive sump drain was, therefore, devised and has proven to be very satisfactory (fig. 1, *A*).

This drain consists of two parts. The outer part is made from a hard rubber tube with an outside diameter of $\frac{1}{2}$ to $\frac{5}{8}$ inches. The lower end of this is rounded with scissors and two holes $\frac{1}{4}$ inch in diameter are cut in the sides, approximately $\frac{3}{4}$ to 1 inch above this. The inner tube consists of a two eyed 16F red rubber catheter, which is slipped down inside the larger tube until the two lower ends coincide. This is the tube which is connected to the suction.

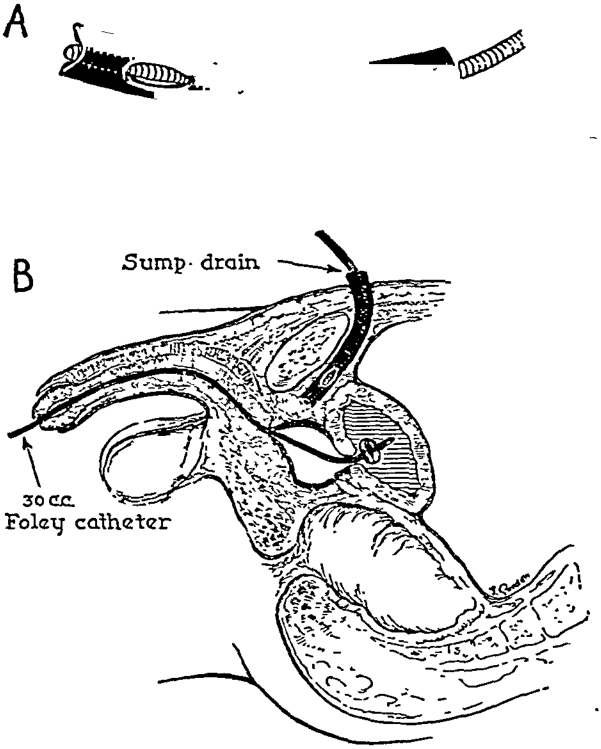

FIG. 1. *A*, construction of sump drain using 18F Robinson catheter and red rubber drainage tube. *B*, sump drain in space of Retzius.

The composite drain is then put down into the space through a stab wound if a transverse skin incision has been used, or through the lower end of a vertical midline incision. In either case the drain should not come in contact with the pubis. It will be found that the hard rubber tubing, which usually has a curve to it, will fit down into the space very readily if the concave side is placed inferiorly (fig. 1, *B*). We prefer the transverse skin incision with a separate stab wound for the sump. We believe that the incision heals better when the drain does not traverse it, and the stab wound itself heals very quickly.

On return to the ward the catheter is attached to the suction apparatus. We have tried various means for applying suction, including central wall suction and Stedman pumps, and have come to the conclusion that the Wangensteen suction is superior to any other. It would seem that this type of drain functions best when connected with suction which is not too strong. Accordingly, the Wangensteen is not allowed to run faster than 100–150 drops per minute.

Following retropubic prostatectomy we have been amazed at the amount of drainage which has resulted. Frequently 200 to 300 cc have been removed in the first 24 hours, and as much as 400 cc in the first 2 days. This has occurred despite the fact that the operative site was "dry" on closure, as evidenced by lack of bleeding and a "watertight" prostatic capsule proven by filling the bladder with irrigating solution.

This procedure has also been very satisfactory following total cystectomy. In these cases the amount of drainage is larger and persists for a longer period of time due to the large raw area resulting after removal of the bladder.

The sump catheter is not irrigated for the simple reason that with continuous suction it is not necessary. The drain will function without irrigation for as long as it is needed, and by eliminating irrigation we also eliminate a possible means of infection.

The entire drain is removed following the first 12 hour period after drainage has stopped. This usually occurs in 48 to 72 hours in the prostatectomy cases, and in 7 to 10 days following cystectomy. The edges of the stab wound are then approximated by an adhesive bridge.

SUMMARY

One of the most frequent complications following retropubic prostatectomy and total cystectomy in this center is a draining suprapubic sinus which, although not serious, has added to the patient's convalescent period.

The use of various types of tube drains has not been satisfactory in correcting this due to the anatomical fact that the space to be drained is at a lower level than the free end of the drain.

A simple, inexpensive type of sump drain is described which has proven to be satisfactory when used with Wangensteen suction apparatus.

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NITROFURAZONE IN TREATMENT OF URETHRO-TRIGONITIS

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In recent years the use of the antibacterial agent nitrofurazone N.N.R.: 5-nitro-2-furaldehyde semicarbazone (furacin R) has met with success in many fields of medicine.[1] The first clinical results were reported in 1945 by Snyder et al.[2] who employed furacin soluble dressing in the treatment of infected war wounds. Since that time many investigations have proven the effectiveness of this drug in the treatment of local infections, but there has been no published report of its use in urinary tract infections. With the development of furacin solution N.N.R., urological application of the drug became possible, and an investigation was begun of its use in the treatment of urethro-trigonitis in women.

METHOD

A total of 63 patients with symptoms of urethro-trigonitis were treated in the out-patient clinic of the University of Tennessee College of Medicine. Forty-three of these patients received furacin therapy, consisting of the instillation of 50 cc of a 1:6 dilution of full strength furacin solution* with sterile, isotonic saline solution into the bladder following catheterization. The patients were instructed to retain the solution for at least 30 minutes before voiding. This procedure was repeated at each of 3 clinic visits over a period of 8 days.

Twenty other patients received instillations of 10 cc of 5 per cent strong silver protein solution in sterile water using a 24F Walther female metal catheter. The treatment schedule was identical with that of the first group.

LABORATORY RESULTS

Bacterial cultures of the urine were made in 20 cases before and after treatment with furacin. In 8 of these, the initial cultures were negative. The sensitivity of the infecting organisms to furacin in the remaining 12 cases was then determined in vitro, using serial dilutions of full strength furacin solution in nutrient broth. The highest dilutions permitting no macroscopic turbidity at the end of 24 hours are shown in table 1.

The time required for furacin to kill bacteria was then determined. The only previously reported investigation of this aspect is by Cramer[3] who found that furacin was bactericidal, rather than merely bacteriostatic, to Micrococcus (Staphlococcus) pyogenes var. aureus within 24 hours. He was using minimal antibacterial concentrations of furacin, such as 1:200,000. However, furacin solution contains nitrofurazone 1:500 and 1:6 clinical dilution of furacin solution used in this study contains 1:2,000. It was believed that the concentrations of nitrofurazone used clinically might be more rapidly bactericidal than those reported by Cramer.[3]

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[1] Daily, L. E.: The nitrofurans. New York State J. Med., 48: 1386, 1948.

[2] Snyder, M. L., Kiehn, C. L. and Christopherson, J. W.: Effectiveness of a nitrofuran in the treatment of infected wounds. Mil. Surg., 97: 380, 1945.

* The furacin solution used in this study was provided by Eaton Laboratories, Inc., Norwich, N. Y.

[3] Cramer, D. L.: The mode of action of nitrofuran compounds. II. Application of physiochemical methods to the study of action against Staphylococcus aureus. J. Bact., 54: 119, 1947.

E. coli was used as the test organism. Serial dilutions of furacin solution in nutrient broth were made, ranging from furacin solution 1:2 in broth, to 1:512. These serial dilutions were inoculated with one loopful of a 24 hour culture of E. coli in broth.

TABLE 1. *Sensitivity of bacteria to diluted furacin solution N.N.R.*

ORGANISM	NO. CASES	MINIMUM BACTERIOSTATIC CONCENTRATION OF FURACIN SOLUTION AT 24 HOURS*
Escherichia coli	6	1:128
Streptococcus faecalis	3	1:128
Pseudomonas aeruginosa	1	1:16
Micrococcus (Staphylococcus) pyogenes var. aureus	3	1:128
Klebsiella pneumoniae	1	1:16
Streptococcus pyogenes (anhemolytic)	2	1:512†
Bacteroides funduliformis	1	No inhibition

* Since furacin solution contains 0.2% nitrofurazone, the minimum bacteriostatic concentration of nitrofurazone may be obtained by multiplying these dilutions by 500, i.e., furacin solution 1:128 = nitrofurazone 1:64,000.

† Maximum dilution used.

TABLE 2. *Bactericidal rate of furacin solution dilutions on E. coli*

TIME OF CONTACT	DILUTION*					
	1:2	1:4	1:8	1:16	1:128	1:512
10 minutes	−	−	+	+	+	+
30 minutes	−	−	−	−	+	+
24 hours	complete inhibition at all dilutions					

+ = growth, − = no growth, on subculturing for 24 hours.

* Multiplication by 500 gives the concentration of nitrofurazone, i.e., 1:2 = 1:1,000.

After 10 minutes, 30 minutes and 24 hours of incubations, subcultures of these inoculated furacin solution dilutions were made, by removing 0.1 cc and adding it to tubes of sterile broth. These were incubated for 24 hours, and at the end of this time the tubes were examined for turbidity. The results, as given in table 2, indicate that a dilution of furacin solution 1:4 is bactericidal for E. coli within 10 minutes and a dilution of 1:16 is bactericidal within 30 minutes.

These results indicate that the 1:6 dilution of furacin solution used clinically, left in the bladder for at least 30 minutes, may be expected to be antibacterial to those susceptible organisms which it contacts.

Previous in vitro studies on an extensive series of organisms have shown that the majority of gram-positive and gram-negative bacteria are sensitive to furacin.[4, 5] Pseudomonas aeruginosa is usually less sensitive than other organisms commonly found in urinary tract infections. It is of interest that one patient of this series was infected by Bacteroides funduliformis which was the only organism whose growth in vitro was uninhibited by full strength furacin solution diluted 1:2 with nutrient broth.

CLINICAL RESULTS

The cases of urethro-trigonitis were divided into two groups (table 3). Group 1 includes all patients in whom the duration of symptoms was less than one month and who had received no previous therapy. Group 2 includes those who had received previous treatment or whose symptoms had been present for longer than one month.

The majority of the cases included in group 1 obtained marked relief of their symptoms, such as dysuria, frequency and urgency, within 48 hours following the first instillation of furacin. The relief following strong silver protein instillation in the group 1 cases was slightly delayed in comparison, but the end results were equally good. None of the patients treated with furacin has had a recurrence of symptoms during the 1 to 9 month follow up period. Some of the chronic cases in group 2 obtained prolonged relief from symptoms for the first time in years.

TABLE 3. *Therapeutic results*

THERAPY	GROUP I			GROUP II		
	Cases	Became Asymptomatic	Failures	Cases	Became Asymptomatic	Failures
Furacin solution	15	15	0	28	22	6
Strong silver protein solution	2	2	0	18	5	13

During the early part of this investigation, a 1:4 dilution of furacin solution in isotonic saline was used. Two patients complained of moderately severe dysuria following the instillation of this strength solution. Since that time the 1:6 dilution of the furacin solution has been employed, and only 3 patients have complained of mild dysuria following the initial instillation.

One patient complained of increased dysuria following the instillation of strong silver protein solution, and in one case of interstitial cystitis, not included in this series, cystoscopic examination revealed argyrosis of the entire vesical and trigonal mucosa. This patient had been treated with strong silver protein solution instillations by a private physician for a period of thirteen years.

On further examination of the 6 patients who did not respond to furacin therapy, 2 were found to have posterior urethral polyps, 2 had persistent upper urinary tract infections, 1 patient failed to complete the prescribed course of

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[4] Dodd, M. C. and Stillman, W. B.: The in vitro bacteriostatic action of some simple furan derivatives. J. Pharmacol. & Exper. Therap., 82: 11, 1944.

[5] Shipley, E. R. and Dodd, M. C.: Clinical observations on furacin soluble dressing in the treatment of surface infections, Surg., Gynec. & Obst., 84: 366, 1947.

therapy after partial relief had been obtained, and 1 required partial resection of a large atonic bladder before relief of symptoms became evident.

Routine urinalyses taken after the completion of therapy revealed no evidence of mucosal irritation due to furacin. This corresponds with the observations of Orcutt,[6] who found that furacin solution, full strength, could be instilled into the bladders of normal rabbits 3 times daily for 14 days without noticeable local effects as determined by macroscopic examination of the bladder mucosa.

Among the patients successfully treated with furacin, none required more than three instillations. The 6 patients who did not respond to furacin therapy were limited to 3 treatments because of the possibility of sensitization, which has been reported when furacin is used for prolonged periods in dermatologic therapy.[7] We observed no symptoms of sensitization in any of our cases.

CONCLUSIONS

Furacin solution appears to be a valuable adjunct in the treatment of urethro-trigonitis in women. In vitro studies have shown it to be rapidly antibacterial in dilutions which cause no irritation or damage to the urinary tract. In this series it brought marked relief to many cases which had proved resistant to previous conservative therapy. While the series studied is not large, it is hoped that the results obtained will encourage further investigation of this drug in the treatment of lower urinary tract infections.

SUMMARY

Forty-three cases of urethro-trigonitis in women were treated by instillations of diluted furacin solution N.N.R. into the bladder. Relief of symptoms was obtained in all acute cases, and in the majority of chronic cases. These results were superior to a comparable series of cases treated with urethral dilatations and strong silver protein solution instillations.

Bacteriological studies disclosed that furacin is bacteriostatic to most organisms which commonly cause urinary tract infections, and rapidly bactericidal to the test bacterium: E. coli.

We express our thanks to Miss Frances Guthrie of the Department of Bacteriology of the John Gaston Hospital for her valuable help in the bacteriological studies.

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the majority of gram-positive and gram-negative bacteria are sensitive to furacin.[4, 5] Pseudomonas aeruginosa is usually less sensitive than other organisms commonly found in urinary tract infections. It is of interest that one patient of this series was infected by Bacteroides funduliformis which was the only organism whose growth in vitro was uninhibited by full strength furacin solution diluted 1:2 with nutrient broth.

CLINICAL RESULTS

The cases of urethro-trigonitis were divided into two groups (table 3). Group 1 includes all patients in whom the duration of symptoms was less than one month and who had received no previous therapy. Group 2 includes those who had received previous treatment or whose symptoms had been present for longer than one month.

The majority of the cases included in group 1 obtained marked relief of their symptoms, such as dysuria, frequency and urgency, within 48 hours following the first instillation of furacin. The relief following strong silver protein instillation in the group 1 cases was slightly delayed in comparison, but the end results were equally good. None of the patients treated with furacin has had a recurrence of symptoms during the 1 to 9 month follow up period. Some of the chronic cases in group 2 obtained prolonged relief from symptoms for the first time in years.

TABLE 3. *Therapeutic results*

THERAPY	GROUP I			GROUP II		
	Cases	Became Asymptomatic	Failures	Cases	Became Asymptomatic	Failures
Furacin solution	15	15	0	28	22	6
Strong silver protein solution	2	2	0	18	5	13

During the early part of this investigation, a 1:4 dilution of furacin solution in isotonic saline was used. Two patients complained of moderately severe dysuria following the instillation of this strength solution. Since that time the 1:6 dilution of the furacin solution has been employed, and only 3 patients have complained of mild dysuria following the initial instillation.

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A NOTE ON THE INACTIVATION BY HEAT OF ACID GLYCEROPHOSPHATASE IN ALKALINE SOLUTION

HELEN QUINCY WOODARD

From the Memorial Hospital Center, New York, N. Y.

In 1946 Herbert reported that, when phenyl phosphate was used as a substrate, the acid phosphatase of the serum of patients with metastasizing carcinoma of the prostate could be inactivated by heating the serum for 1 hour at 37 C prior to adding it to the substrate. She pointed out that the effect was due to the alkaline pH of the serum, and that the acid phosphatase of extracts of prostatic tissue could also be inactivated by heating at 37 C at pH 7.4 but not at pH 4.8. As the behavior of phosphatases in different substrates varies considerably, I decided to determine whether the activity of acid phosphatases with respect to sodium beta glycerophosphate was similarly affected by heating in alkaline solution, and, if so, whether the sensitivity to heat was great enough to constitute a source of error at room temperature in summer.

The acid phosphatase activities of serum or of extrcts of tissue were determined by the method previously described, sodium beta glycerophosphate being used as substrate. Specimens of serum or tissue extract were placed in water baths at various temperatures for 10 to 60 minutes, control portions being held in an ice bath. At the end of the period of heating the heated specimens were chilled in the ice bath. They and the controls were then added to warmed substrate, and the phosphatase activities at pH 4.7 to 5.2 were determined in the usual way.

The results of experiments with serum are summarized in table 1. For convenience in obtaining sufficient serum for a large experiment several specimens from men know to have elevated acid phosphatase readings or from females were pooled, and the pools kept in the ice box for varying periods, usually 24 to 48 hours, but sometimes longer. The initial acid phosphatase readings of the male serum pools ranged from 2.7 to 13.7 units/100 cc, and those of the female serum pools from 0.2 to 0.4 units/100 cc. Normal values for serum acid phosphatase as found in this laboratory are from 0 to 0.9 units per 100 cc. It is evident that the acid glycerophosphatase activity of the serum from patients with metastasizing carcinoma of the prostate was almost completely abolished by heating for 1 hour at 37 C. The effect of heat was appreciable in 30 minutes at temperatures as low as 28 C, and became serious at 30 C. The acid phosphatase activity of female serum was also diminished by heating, although the initial activity was so low that the changes were not of quantitative significance. The pH of serum increases rapidly on standing, refrigerated specimens reaching pH 8.0 to 8.5 in the first 24 hours, and changing slowly thereafter. Hence four specimens of serum from patients with metastasizing carcinoma of the prostate and acid phosphatase readings of 1.8 to 22.0 units/100 cc were tested for heat sensitivity within 2 hours after the blood was drawn. As is shown in table 1, the heat sensitivity, although less than in preserved serum, is still marked.

TABLE 1. *Effect of heating on the acid phosphatase activity of serum*

SOURCE OF SERUM	NO. EXPTS.	TEMP. C	TIME OF HEATING, MINUTES	% ACID P-ASE ACTIVITY REMAINING
Pooled preserved serum from patients with ca. of prostate	3	37	60	0 to 4
Pooled preserved female serum	6	37	60	0 to 39
Fresh serum from patients with ca. of prostate	4	37	60	13 to 25
Pooled preserved serum from patients with ca. of prostate	1	28.0	30	75
		28.5	30	63
Pooled preserved serum from patients with ca. of prostate	1	30	15	73
		30	30	64
		30	45	49
		30	60	38
Pooled preserved serum from patients with ca. of prostate	1	37	10	2.2
			20	1.9
			30	1.9

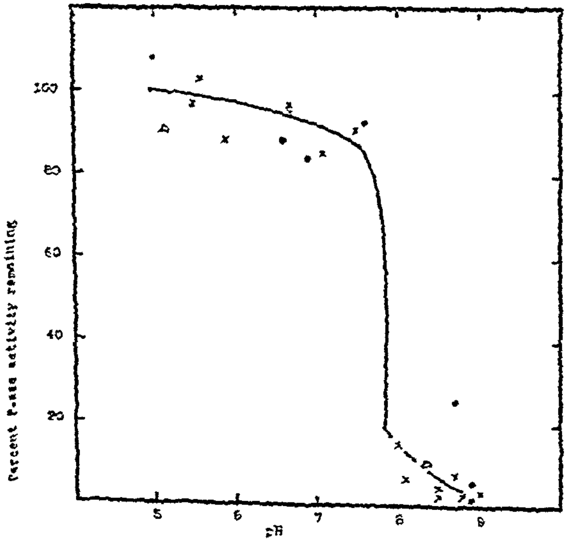

FIG. 1. Percentage of acid glycerophosphatase activity remaining in extracts of human prostatic tissue and rat liver tissue after heating for 1 hour at 37C, plotted against the pH of the solution during heating. X = extract prostatic tissue; Δ = extract prostatic tissue mixed with female serum. ● = extract liver normal rat.

Since the acid glycerophosphatase of female serum was found to be inactivated by heating in alkaline solution, it was evident that this behavior is not peculiar to acid glycerophosphatases of prostatic origin. Hence another acid phosphatase, that of extract of normal rat liver, was tested and found to be inactivated by heating to 37C in alkaline solution. The heat sensitivity of acid phosphatases over a considerable pH range was tested by bringing portions of two extracts of normal rat liver, one extract of normal human prostatic tissue, and one extract of a human prostate which had undergone benign hypertrophy to various pH values by the addition of small amounts of hydrochloric acid or sodium hydroxide, and then heating at 37C for 60 minutes. The extracts were also tested at their natural pH of 6.5 to 7.0. Control portions at the same pH were held in an ice bath. The phosphatase activities were then determined at pH 4.7 to 5.2. In figure 1 the per cent of phosphatase activity remaining after heating is shown plotted against the pH at which the extracts were heated. It is seen that the acid glycerophosphatases of human prostate and of rat liver are only slightly inactivated by heating at pH values between 5.0 and 7.5, but become very thermolabile in more alkaline solutions. Extracts of prostatic tissue mixed with female serum did not differ conspicuously in heat sensitivity from prostatic extract alone at the same pH.

The results of other experiments indicated that the acid phosphatase activity of extracts of prostatic tissue was not affected by holding for 3 weeks in the ice box at pH values between 8.0 and 8.8, and that the thermolability of such extracts was lost immediately when they were acidified.

SUMMARY

The acid glycerophosphatases of the serum of human females, of males with metastasizing carcinoma of the prostate, and of extracts of human prostatic tissue and of rat liver tissue are nearly or quite completely inactivated by heating for one hour at 37C at a pH of 8.0 or above. Significant inactivation of the acid phosphatase in the serum of patients with metastasizing carcinoma of the prostate may take place in 30 minutes at 28C, and may lead to serious errors in determinations made in warm weather.

REFERENCES

HERBERT, F. K.: The estimation of prostatic phosphatase in serum and its use in the diagnosis of prostatic carcinoma. Quarterly J. Med., **15**: (new series) 221–241, 1946.

WOODARD, H. Q.: Acid and alkaline glycerophosphatase in tissue and serum. Cancer Research, **2**: 497–508, 1942.

THE JOURNAL OF UROLOGY
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SCIENTIFIC PROGRAM, ANNUAL MEETING, MID-ATLANTIC SECTION, AMERICAN UROLOGICAL ASSOCIATION

Chamberlain Hotel, Old Point Comfort, Va., April 12 to 14, 1951

THURSDAY, APRIL 12

PEDIATRIC UROLOGY: DIAGNOSTIC AND OPERATIVE PROBLEMS, Seymour W. Rubin and John A. Askin (by invitation), Baltimore, Md. Discussion, David M. Davis, Philadelphia, Pa.

TREATMENT OF CARCINOMA OF THE MALE URETHRA BY RADICAL INFRAPUBIC REMOVAL, Edward D. Holfelner (by invitation), Charles A. W. Uhle, Philadelphia, Pa. Discussion, Charles H. deT. Shivers, Atlantic City, N. J.

TRIPLICATION OF THE URETER AND RENAL PELVIS, Richard D. Gill, Wheeling, W. Va. Discussion, Ralph R. Landes, Danville, Va.

RETROPERITONEAL DISSECTION IN TESTICULAR TUMORS: THE NAGAMATSU TECHNIQUE, Brice S. Vallett, Wilmington, Del. Discussion, Lloyd G. Lewis, Washington, D. C.

CARCINOMA OF THE PROSTATE IN YOUNG ADULTS: REPORT OF TWO CASES, Col. James C. Kimbrough and Captain Evan L. Lewis (by invitation), Washington, D. C. Discussion, Edward W. Campbell, Philadelphia, Pa.

URETERAL MANAGEMENT FOLLOWING REMOVAL OF THE BLADDER AND LOWER BOWEL FOR CARCINOMA, Lowrain E. McCrea, Philadelphia, Pa. Discussion, Captain Harold J. Cokely, U. S. N. Hospital, Bethesda, Md.

FRIDAY, APRIL 13

MANAGEMENT OF TRAUMA TO THE URETHRA, S. W. Mulholland, Philadelphia, Pa. and Harry M. Madonna (by invitation) Philadelphia, Pa. Discussion, R. Carl Bunts, Richmond, Va.

EXPERIMENTAL AND CLINICAL APPLICATION OF THE ARTIFICIAL KIDNEY, Albert E. Goldstein and (by invitation) M. Golden, M. Ruben, H. Silverstein, Baltimore, Md.

ACUTE ANURIA. REMARKS ON THE NATURE OF THE RENAL LESION AND THE USE OF THE PERITONEUM FOR DIALYSIS, Robert A. Kelley (by invitation), Charlottesville, Va. Discussion of these two papers to be opened by Charles P. Howze, Washington, D.C. and Leon Herman, Philadelphia, Pa.

EPISPADIAS WITH INCONTINENCE, Hugh Warren, Charlottesville, Va. Discussion, Walter W. Baker, Philadelphia, Pa.

A CONCEPT CONCERNING TREATMENT OF EXSTROPHY OF THE BLADDER, William H. Boyce (by invitation), and Samuel A. Vest, Charlottesville, Va.

EXSTROPHY OF THE BLADDER. SURGICAL TREATMENT BY EXTRAPERITONEAL TRANSPLANTATION OF THE DIVIDED TRIGONE INTO THE RECTUM, Willard E. Goodwin, Baltimore, Md. and Perry B. Hudson (by invitation), New York. Discussion of these two papers to be opened by Austin I. Dodson, Richmond, Va. and John A. C. Colston, Baltimore, Md.

SATURDAY, APRIL 14

PRESIDENTIAL ADDRESS: CARCINOMA OF THE URETER, Albert A. Creecy, Newport News, Va.

GUEST SPEAKER: THE FUSED KIDNEY: SURGICAL EXPOSURE AND MANAGEMENT, Robert Boyd McIver, M.D., Jacksonville, Florida

HYDATID DISEASE OF THE KIDNEY: REPORT OF A CASE, William Baurys, Sayre, Pa. Discussion, John H. Hoskins, Lynchburg, Va.

SUSCEPTIBILITY OF PLEUROPNEUMONIA-LIKE ORGANISMS TO STREPTOMYCIN AND TERRAMYCIN, Paul R. Leberman and (by invitation) Paul F. Smith and Harry E. Morton, Philadelphia, Pa. Discussion, Austin Wood, Baltimore, Md.

PROGRESS IN THE SUPRAPUBIC METHOD OF PROSTATECTOMY, Joseph C. Birdsall, G. C. Poore and (by invitation) H. M. Burros and D. Liang, Philadelphia, Pa. Discussion, W. H. Toulson, Baltimore, Md.

SYMPTOMS OF UPPER URINARY TRACT DISEASE SIMULATING HERNIATED INTERVERTEBRAL DISC, Maxwell Malament and R. Carl Bunts, Martinsburg, W. Va. Discussion, Herbert D. Wolff, Jr., Alexandria, Va.

AORTOGRAPHY AND ARTERIOGRAPHY BY PERCUTANEOUS CATHETERIZATION OF THE FEMORAL ARTERY IN THE DIAGNOSIS OF RENAL DISEASES, B. S. Abeshouse and I. Scherlis (by invitation), Baltimore, Md. Discussion, William P. Herbst, Washington, D. C.

SCROTAL URETER, Hugh J. Jewett, Baltimore, Md., and A. Page Harris (by invitation), Baltimore, Md. Discussion, Grattan G. Irwin, Charleston, W. Va.

MEETING OF NEW YORK SOCIETY
AMERICAN UROLOGICAL ASSOCIATION

April 15, 1951

Yale Club, New York, N. Y.

8:30 P.M. PAPER OF THE EVENING:

Dr. Ormond S. Culp, Mayo Clinic, Rochester, Minn.

The Prevention of Pulmonary Emboli

MEETING OF NEW ENGLAND SECTION
AMERICAN UROLOGICAL ASSOCIATION

April 12, 1951

New Haven, Conn.

Afternoon program at New Haven Hospital.

Evening program at Hotel Taft. The speaker will be Dr. Archie L. Dean of New York City. The title of his address will be "Surgical Treatment of Tumors of the Genito-Urinary Organs."

THE JOURNAL OF UROLOGY
Vol. 65, No. 5, May 1951
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TERATOID TUMORS OF TESTIS

ROBERT A. MOORE

From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo. and the Armed Forces Institute of Pathology, Washington, D. C.

It is appropriate that the American Urological Association sponsor the Ramon Guiteras lecture at a time when international viewpoint bids fair to be the very basis of continuance of our free democratic world, and in this capitol city of Washington. Dr. Guiteras, after graduation from medical schools, studied for 2 years in the medical centers of Europe. Each year throughout his life he traveled to some country in order to learn more of the life, customs, and ideals of other peoples. Guiteras, bearing a Spanish name, but born in Rhode Island, was a true internationalist. It is a privilege and an honor to give the lecture established in memory of one of the founders of this association.

The story which I wish to tell you today began in 1862, when Surgeon General W. A. Hammond established the Army Medical Museum as a central repository for anatomic and pathologic material from the personnel of the Army. Under various Surgeons General, various curators, and various regulations a considerable volume of material was accessioned during the following sixty years.

After World War I, under the able leadership of George R. Callender, now a retired Brigadier General, new regulations were approved, and the objectives of the Museum were reoriented in the direction of research rather than that of simple accumulation of specimens for cataloging and display. However, the high ideals in this field suffered the same fate that other ideals did in the 1920's and 1930's.

With the enactment of the original draft law in 1940 and our subsequent entry into World War II as a combatant, the number of specimens received increased in geometric ratio to time. It was apparent that within a few years there would be a collection of pathologic specimens unequaled any other place in the world. The then director James E. Ash, now a retired Colonel, and his deputy Balduin Lucké, now the professor of pathology at the University of Pennsylvania, determined on a policy of organization and viewpoint which would not only handle the routine of the day, but make possible extensive research activities. One step to effectuate this program was a change in name from Army Medical Museum to Army Institute of Pathology.

It was my good fortune in 1942 to be asked by Col. Ash and Col. Lucké to undertake a comprehensive study of testicular tumors. This was initiated in collaboration with Nathan B. Friedman, then a Major stationed at the Institute, and now director of laboratories at the Cedars of Lebanon Hospital in Los Angeles. During the past two years through the courtesy of the present director, Brig. Gen. Raymond O. Dart, and in cooperation with the National Research

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The Ramon Guiteras lecture read at annual meeting, American Urological Association, Washington, D. C., May 31, 1950.

Work supported in part by Veterans Administration.

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Council and the Veterans Administration, Dr. Frank Dixon, an assistant professor of pathology at Washington University, has reviewed all the pathologic material and carried out a follow-up study to evaluate prognosis in terms of many factors.

There are two types of discussion I could present: a general review of the present knowledge of testicular tumors, or a consideration of a few topics with which I have had personal experience. I have assumed that you wish me to follow the latter course. At this point I desire to extend my apologies to the many investigators who have made notable contributions to the subject for not mentioning their work. Little that I shall say is truly original. Scientific knowledge is built brick upon brick and only rarely does someone strike out into a completely new field or concept.

GENERAL INCIDENCE OF INTRASCROTAL TUMORS

On December 31, 1947, there were 1106 intrascrotal tumors on file at the Institute, which came from Army personnel, a series far larger than has been available previously for investigation. Dr. Dixon's studies and any statements I make today are based on this group of tumors. All of our studies are not completed and some statistical analyses will be based on only a part of the series; but in every instance a consecutive part beginning with the first tumor.

It should be emphasized that the incidence of testicular tumors is no higher in personnel of the Army than in the civilian populations. There are three reasons why so many tumors have been collected at the Institute: first, the peak age incidence of testicular tumors is 18 to 40; second, from 1941 to 1946 a significant fraction of men of this age were in the United States Army; and third, there was and is an Army regulation which requires forwarding of all pertinent pathologic specimens to the Institute from every Army installation.

Interest in testicular tumors, both theoretically and practically, is focused on the group known as teratoid tumors. Inasmuch as the specimens at the Institute include all testicular tumors, the first step was to separate the teratoid from the other tumors. Gross and histologic study of the 1106 intrascrotal tumors shows the accompanying distribution by groups (table 1). In other words, given an intrascrotal tumor there is an 89.6 per cent probability it is a teratoid tumor.

CELLULAR TYPES OF TERATOID TUMORS

My experience in the classification of teratoid tumors of the testis has been essentially the same as that of most other students of this problem. After a review of the first 25 cases, I was certain there were 25 different types. But with 50 cases some of the difficulties were resolved, and I concluded that there were perhaps only 40 different kinds. With 100 tumors the problem was still clearer and I believed there were at the most 10 varieties. At the present time, I believe there are 4 basic types of teratoid tumors and on some days I would be satisfied with 3.

The 4 basic cellular types are: adult teratoma, seminoma, embryonal carcinoma and choriocarcinoma. In a classification of 3 types the latter two are combined as trophoblastoma.

Adult teratoma. The adult teratoma is typically a moderate-sized tumor composed on the cut section of firm gray-white tissue containing cystic spaces, small yellow or white foci of epithelium, and islands of blue translucent cartilage. It is sharply circumscribed from the surrounding compressed testicular tissue.

Microscopically there is great variability of cellular and tissue elements, but all the elements are organized. For example, epithelium does not grow irregularly through the supporting fibrous tissue as does the epithelium of a carcinoma. but the cells, squamous or columnar, are oriented to one another and to a surface, a glandular space (fig. 1), or to an architectural pattern similar to that of some normal structure. Further, there is organization between different cellular types. About many cystic spaces lined with columnar cells there is a zone of connective tissue: mucosa, and a zone of smooth muscle, muscularis, simulating some hollow viscus of the body. About spaces lined with squamous epithelium there are at times hair follicles, sweat glands, and sebaceous glands, to duplicate exactly the normal skin.

TABLE 1. *Incidence of testicular tumors*

	NUMBER	
Tumors of testis proper		1032
Teratoid tumors	991	
Interstitial cell tumors	10	
Miscellaneous tumors	31	
Tumors of appendages		74
Epididymis	46	
Cord	26	
Total		1106

Seminoma. The seminoma is characteristically a small to moderate sized tumor. The neoplastic tissue is gray, and soft, and bulges from the cut section. Although the tumor is circumscribed, it is not encapsulated. There are only rarely foci of necrosis and hemorrhage.

The basic architectural pattern observed microscopically is that of irregular sheets and islands of seminoma cells separated by connective tissue trabeculae (fig 2). The typical seminoma cell is round or polygonal and 15 to 25 microns in greatest dimension. The cell wall is prominent and the nucleus occupies about half the cell. The cytoplasm varies from a completely clear type to a dense deeply eosinophilic variety. During mitotic division hyaline droplets are present in the cytoplasm. The nucleus is moderately chromatic and contains one or more conspicuous nucleolar masses.

The connective tissue trabeculae are infiltrated with a variable number of lymphocytes, plasma cells and eosinophilic leukocytes. At times the lymphocytes are organized into a lymphoid follicle. The connective tissue is moderately cellular with only a minimum of collagen.

Near the edges of some seminomas there are small granulomatous masses, sometimes mistaken for the tubercle of tuberculosis. They are probably alterations in seminiferous tubules which have been invaded and surrounded

In the adjacent testicular tissue, cells similar to or identical with the seminoma cells line or fill seminiferous tubules. The seminoma of the testis is identical with the tumor of the ovary usually called dysgerminoma.

Embryonal carcinoma. This tumor is usually a large bulky tumor with complete invasion or destruction of the normal testes and of the appendages. On the cut section there is a gray soft tissue containing many foci of necrosis and hemorrhage.

The architectural pattern is that of variable sized lobules of neoplastic cells separated by a dense connective tissue stroma infiltrated with a few lymphocytes.

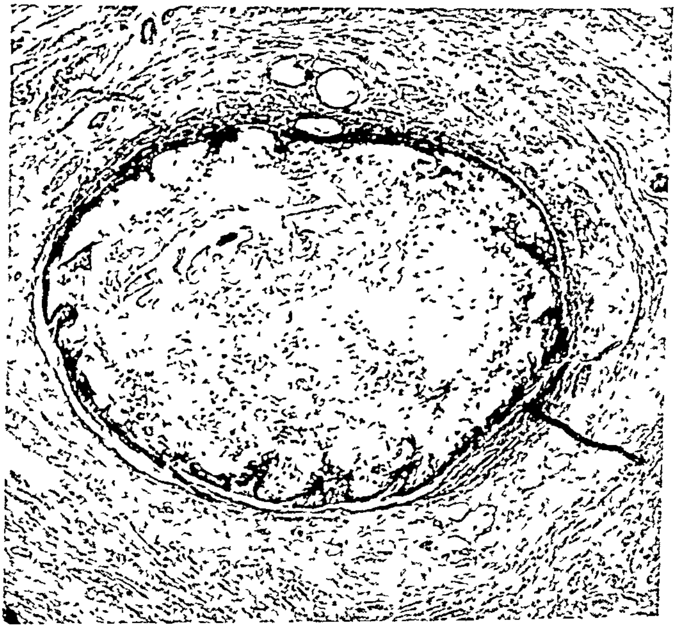

FIG. 1. Adult teratoma showing organization of columnar epithelium and smooth muscle.

The neoplastic cells vary greatly in pattern but the individual cells have many features in common. The cells are irregular in size and shape and cell walls are inconspicuous. The cytoplasm is palely basophilic and reticulated. The nuclei are lightly chromatic and highly anaplastic with marked differences in size, shape, and density of chromatin Some cells are multinucleated (fig. 3, *A*).

In some tumors the cells are arranged in small solid lobules, while in others vacuolation of cells and coalescence of vacuoles leads to a cystic, papillary, or complex pattern.

In about one third of embryonal carcinomas there is a second cellular type, apparently differentiated from the first. This cell typically is observed at the edges of the lobules It is elongated or stellate, and the cytoplasm is denser and more deeply basophilic (fig. 3, *B*). Many cells are multinucleated and the nuclei are more chromatic than those of the other cells. Frequently this second cell surrounds one or two of the first cells as in a sheath.

The appearance of the two cellular types is reminiscent of the early stages of development of the placental trophoblasts. It must remain for the future to determine if all embryonal carcinomas are in fact trophoblastomas. If true, they should be so named as trophoblastomas or more specifically cytotrophoblastomas.

Choriocarcinoma. The choriocarcinoma, the most malignant of all testicular tumors, is usually a small tumor. It is soft in consistency and on the cut section little but a soft hemorrhagic mass is observable.

Two cellular types are identifiable microscopically; cytotrophoblasts and syncytiotrophoblasts. The cytotrophoblasts are identical with the cells of the cytotrophoblastoma (fig. 4).

The syncytiotrophoblast is a large cell, 50 to 500 microns in greatest dimension. The cytoplasm is lightly eosinophilic or amphophilic and is finely vacuolated. The cell wall is indistinct and pseudopodia of cytoplasm extend into the surrounding tissue. There are multiple nuclei which vary from large lightly chromatic forms to smaller deeply chromatic types, but all the nuclei in any one cell are the same. There is frequently hemorrhage about the syncytiotrophoblasts.

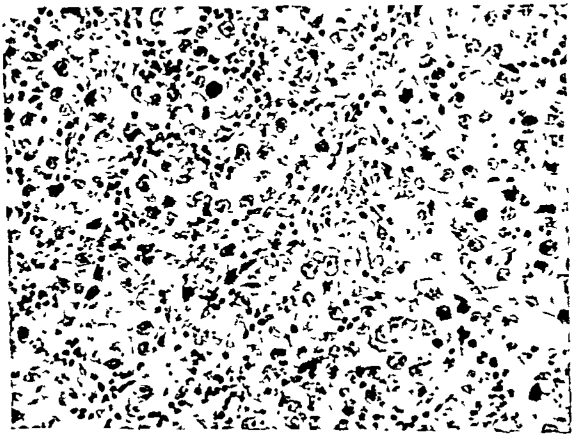

FIG. 2. Seminoma

The two cells, cyto- and syncytiotrophoblasts may be arranged without orientation to one another or may be organized into structures identifiable as chorionic villi.

COMPLEX TUMORS

On the basis of the description of these 4 cellular types, it might be concluded there are 4 teratoid tumors of the testis. This, however, is not a proper conclusion. There are 4 cellular types, but not 4, but 12 different tumors; 12 because each cellular type occurs singly and in combination with any one, two, or three of the other 3.

Thus, in 237 tumors of this series a total of 368 cellular types were observed, or 1.5 types per tumors (table 2).

However, the combinations follow a definite pattern and do not occur at random or by probability of frequency of the single types. In the same group of 237 tumors the association of two cellular types was as shown in table 3.

My interpretation of this selective association is that there are definite lines of origin and differentiation of each cellular type, a topic to be fully discussed in a later section.

From a practical standpoint the known occurrence of tumors with multiple cellular types is important. Each cellular type has an influence on prognosis, and the overall prognosis of any given tumor is that of the most malignant type present. Hence, testicular tumors should be thoroughly examined grossly for all variations of structure. One knife cut through the center of the tumor is not adequate. In one small region of an adult teratoma there may be a focus of embryonal carcinoma and the five year survival rate drops from an average of 75 per cent to not over 30 to 50 per cent.

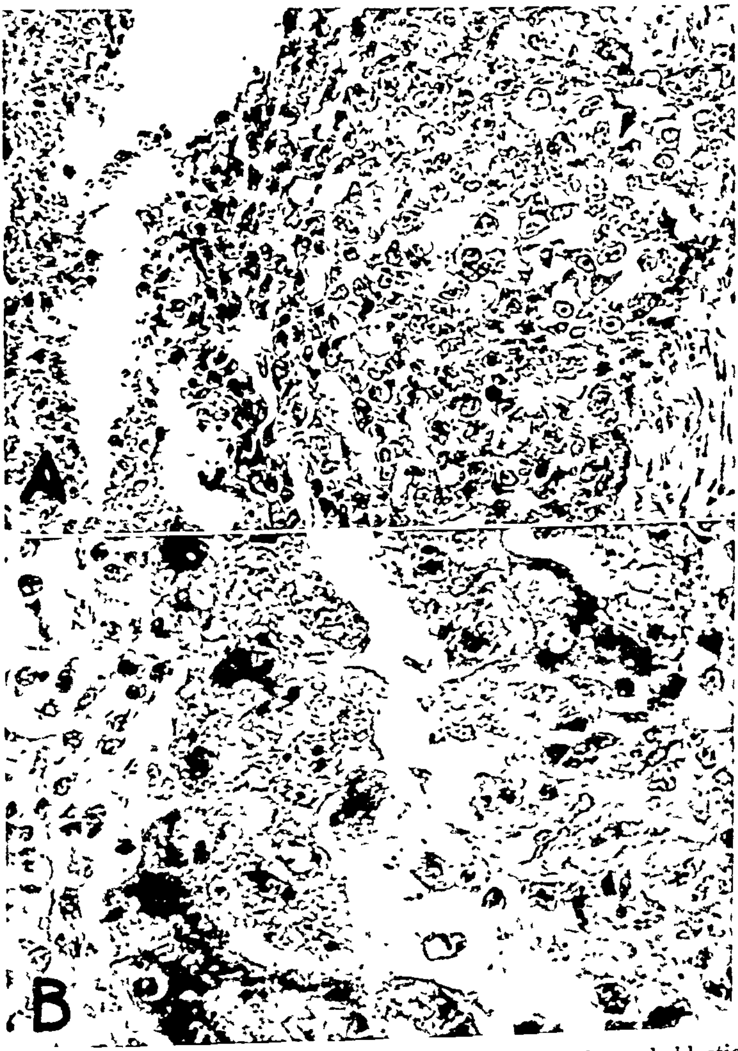

FIG. 3. *A*, embryonal carcinoma *B*, embryonal carcinoma with trophoblastic change

PROGNOSIS

The classification of testicular teratoid tumors based on 4 cellular types is not only histologically sound, but in the few instances in which it has been used in evaluation of prognosis, it has proved satisfactory.

The follow-up studies on the present series have not been completed by Dr. Dixon, and hence I can not give you details. However, I can give you two general statements. First, with a follow-up period of 2 to 10 years, 50 per cent of all patients are dead of tumor. And, second, 95 per cent of all deaths occurred within 2 years. Sometime in the next year Dr. Dixon will publish the results of his investigation and many correlations will be available so an accurate prognosis may be made on any given tumor.

Since 1946, when Friedman and I proposed the present classification, Lewis in a study of 200 of the tumors included also in our series, and Sauer, Watson, and Burke at the New York State Institute, have collected figures on prognosis (table 4).

TREATMENT

It is not proper that a pathologic anatomist discuss fully treatment, but there are observations in pathology which have a bearing on some aspects of treatment.

TABLE 2. *Cellular types in 237 testicular tumors*

Adult teratoma	108
Seminoma	100
Embryonal carcinoma	144
Choriocarcinoma	16

First, the results of the follow-up studies indicate that all tumors of the testis, even those which have the histologic appearance of a benign tumor, are actually malignant or potentially so. Hence, all tumors of the testis should be treated as malignant tumors.

Second, all tumors including the adult teratoma may invade the cord and, therefore, if surgery is the method of primary treatment, the cord should be removed. Further, there is some evidence that the seminoma cell may infiltrate the finer lymphatics and tissue spaces of the tunica and the cord. Therefore, all tissue about the cord should be removed, especially if the cellular type of the tumor is seminoma.

Third, the embryonal carcinoma and the choriocarcinoma are composed of cells which have the capacity to invade blood vascular spaces. Hence, any treatment directed to removal of the draining lymph nodes will not be as successful as with somatic carcinoma in which vascular invasion is less common.

Fourth, the radiosensitivity of the 4 cellular types varies greatly. The seminoma is highly sensitive, the embryonal carcinoma moderately sensitive, and the adult teratoma and choriocarcinoma highly resistant. Hence, before radiation therapy is given, the cellular type or types present should be determined by removal of the primary tumor.

Fifth, the known higher incidence of a tumor in the remaining testis, especially if it is ectopic, after one has developed raises the question of preventive surgery. The figures given by Gilbert and Hamilton certainly support careful consideration of the desirability of bilateral orchiectomy in the treatment of testicular tumors when the remaining testis is ectopic.

The choice of treatment is between surgery or radiation or some combination. I shall not enter the controversy between exponents of one or the other except to make three general observations. First, I doubt that with present techniques all neoplastic tissue of a testicular tumor within the abdomen or thorax can be completely eradicated by radiation short of serious injury to normal structures. In some patients definite alleviation can be accomplished by radiation. Second, I see no advantage of preoperative radiation, and it has the disadvantage of delaying surgical removal. Third, the radical surgical procedure with removal of the lymph nodes as high as the renal artery is logical, but the operation is difficult and the mortality is high except in the hands of a few. It may be worth while with the radioresistant tumors.

TABLE 3. *Association of two cellular types in 237 testicular tumors*

	ADULT TERATOMA	SEMINOMA	EMBRYONAL CARCINOMA	CHORIOCARCINOMA
Adult teratoma	—	1	69	2
Seminoma	1	—	13	0
Embryonal carcinoma	69	13	—	4
Choriocarcinoma	2	0	4	—

TABLE 4. *Prognosis on testicular tumors; five year survival rate, per cent*

	LEWIS	SAUER, WATSON AND BURKE
Adult teratoma	75	75.0
Seminoma	84	57.4
Embryonal carcinoma	65	35.7
Choriocarcinoma	16	33.0

RELATION TO URINARY GONADOTROPIN

In the late 1920's a definite relation between increased amounts of urinary gonadotropin and the presence of a testicular tumor was established. However, in the first flush of discovery too broad a generalization was made and too detailed a relation of histologic structure to amount of hormone was postulated. In the minds of many the whole concept of a relation was, therefore, discredited.

In the study of the material at the Armed Forces Institute of Pathology we have had no opportunity to carry out personal studies of the urinary gonadotropin. However, we have had available the results of some tests. Further, we have developed certain ideas concerning the nature of the cell of the teratoid tumor. The results of the tests and our ideas about the cell fit well with the

conclusions of Twombly on the relation of the tumors to gonadotropin and I venture to present them to you.

In many, but not all tumors which are generally called embryonal carcinomas, there is a second type of cell. Particularly at the edge of a lobule of neoplastic cells in contact with the connective tissue stroma, there are elongated larger cells with a deeply basophilic cytoplasm and prominent chromatic nuclei (fig. 3, *B*). At times there is multinucleation and the cytoplasm may be finely vacuolated.

If this type of basophilic elongated cell and the association with other cells is compared to the early stages of the development of the mammalian placenta, there is striking similarity or practical identity. The basophilic cell is the primitive syncytiotrophoblast and the bulk of the cells is the cytotrophoblast.

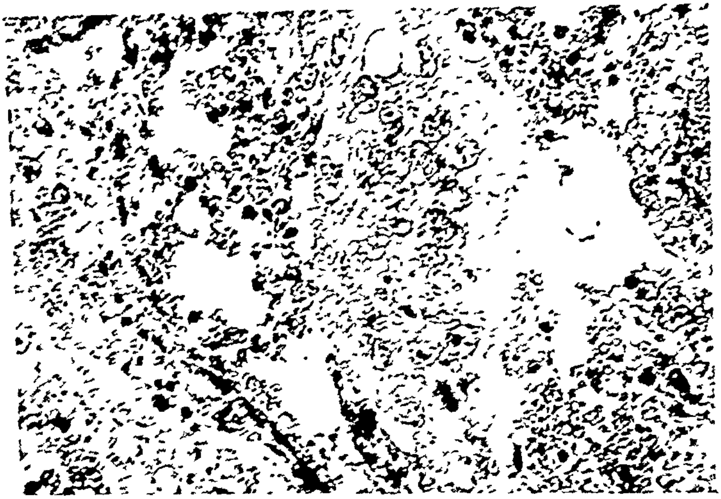

Fig. 4 Choriocarcinoma

This comparison is one of the factors which has led me to believe that many, if not all, embryonal carcinomas are in fact tumors of the primitive cells of the placenta, the cytotrophoblasts.

From tissue culture studies and quantitative estimation of the urinary gonadotropin at various times during pregnancy in relation to relative numbers of cyto- and syncytiotrophoblasts, it is apparent that gonadotropin is elaborated by cytotrophoblasts.

If these conclusions be correct, then the relation of certain testicular tumors to excessive urinary gonadotropin is clear. Some tumors of the testis are composed of the neoplastic counterpart of the normal cell of the placenta which secretes gonadotropin. Hence, there is every reason to expect that a patient with this tumor would have excessive amounts of gonadotropin in the urine.

Inasmuch as it is fully accepted that the choriocarcinoma contains the same cell, the cytotrophoblast, I need not elaborate on why patients with this tumor have excessive amounts of gonadotropin in the urine.

On the other hand, a rare patient with a seminoma excretes excessive amounts

Fifth, the known higher incidence of a tumor in the remaining testis, especially if it is ectopic, after one has developed raises the question of *preventive surgery*. The figures given by Gilbert and Hamilton certainly support careful consideration of the desirability of bilateral orchiectomy in the treatment of testicular tumors when the remaining testis is ectopic.

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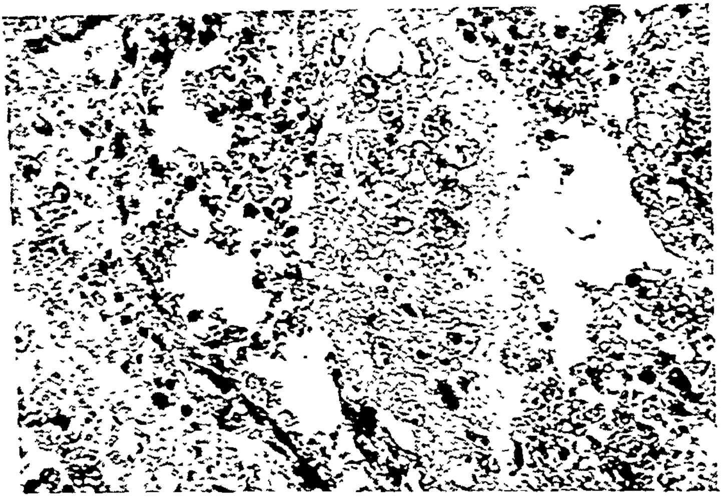

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INDUCTION AND ORGANIZATION IN SOMATIC ELEMENTS

On superficial examination the impression is secured that the somatic elements in the teratoid tumors are arranged irregularly and without an organoid pattern. After careful study this is still true in part, but it becomes more and more apparent with continued observation that one type of cell or tissue is in geographic relation to another type of cell or tissue.

For example, many glandular acini lined with columnar cells are surrounded by a definite layer of smooth muscle (fig. 1). At times the subepithelial tissue is loose and infiltrated with lymphocytes, the epithelium is ciliated, and outside the muscle are plates of cartilage. This is the organoid structure of a bronchus. In others, the epithelium is mucus-secreting and the muscle is arranged in two layers duplicating the layers of the small or large intestine (fig. 6). It is of more than passing interest that the intestinal mucosa in teratoid tumors is infiltrated with eosinophiles indicating that this cell is an integral part of the intestine and not a response to the content.

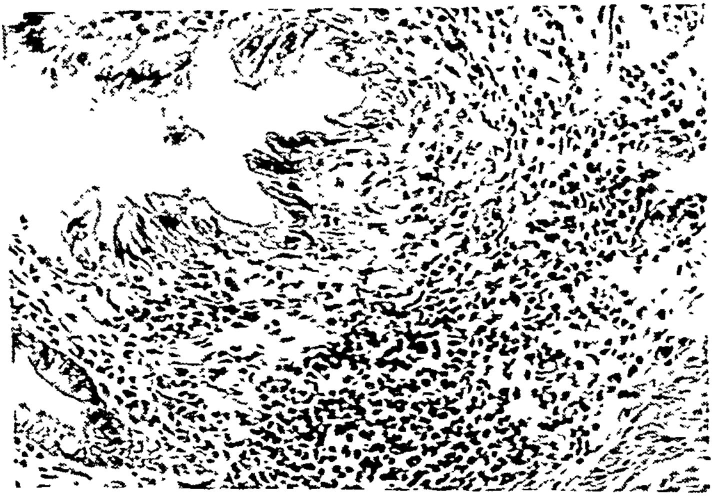

FIG. 6. Organoid pattern of a segment of the small intestine in an adult teratoma

Rarely a space between two pieces of cartilage exactly duplicates a joint space and synovial villi (fig. 7). Within trabeculae of bone there may be immature or fully developed bone marrow.

These observations indicate that the same factors which are responsible for organization of the normal embryo are operative in part in the teratoid tumors. I bring this aspect before you not for any immediate practical importance, but to suggest first that further study of it may give clues on possible therapeutically induced organization as a form of treatment, and second that detailed investigation of this phase of teratoid tumors may well reveal facts of embryology not demonstrable in the normal fetus.

Of great significance in an evaluation of the nature of teratoid tumors is the finding of adult teratomatous elements in the cord (fig. 8) or in metastases; so of urinary gonadotropin. Correspondingly a rare example of seminoma contains large typical syncytiotrophoblasts with vascular spaces within the cytoplasm (fig. 5). Unless differentiation in the trophoblastic series is different in neoplasms from that in the normal placenta, this observation proves that the seminoma cell is potentially a cytotrophoblast. Hence, it is not unreasonable to believe that at times the seminoma cell might secrete excessive amounts of gonadotropin.

So much for our own observations and deductions on this topic; how do these fit into the results of others, notably those of Twombly? The most important observation is that patients with a testicular tumor may and frequently do have two types of gonadotropin in the urine, pituitary and chorionic. With tests capable of distinguishing between the two types, it can be readily shown that first, all patients with a testicular tumor regardless of cellular type have a slight but definite increase of urinary pituitary gonadotropin, and second, that only some patients with testicular tumors have excessive amounts of chorionic gonadotropin in the urine.

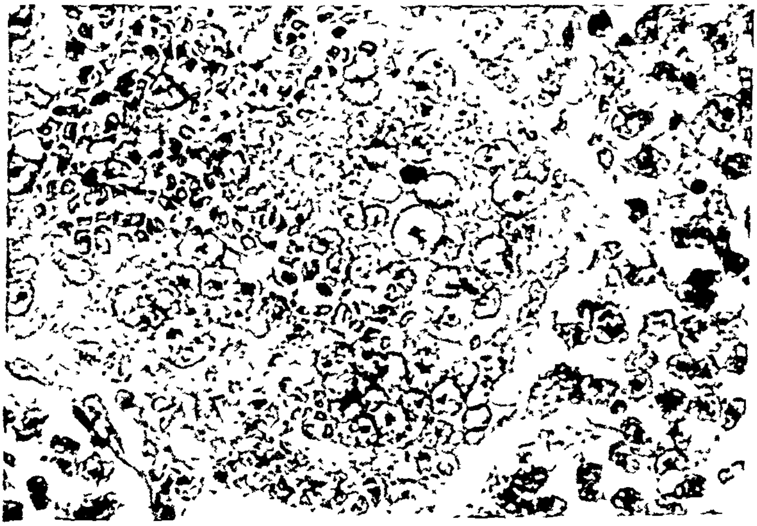

FIG. 5. Syncytiotrophoblasts in a seminoma

There is not yet sufficient correlative evidence for a definitive statement, but I suspect that those testicular tumors associated with chorionic gonadotropin include all choriocarcinomas, most embryonal carcinomas, and the rare seminoma with trophoblastic tendencies.

The practical point which stems from these endocrinologic and histologic studies is that detection of the presence and the amount of urinary gonadotropin may be helpful in the diagnosis and evaluation of prognosis of a patient with a testicular tumor provided a distinction is drawn between pituitary and chorionic gonadotropin. If a relatively sensitive test is used both types will be demonstrated, while if a less sensitive test is used the slightly excessive pituitary gonadotropin will be undetected and only the chorionic type revealed. I believe that these facts explain in large part the great discrepancy in reported results on the relation of gonadotropin to testicular tumors.

Fourth, there are the well known instances of widespread metastases of a choriocarcinoma without a palpable tumor of the testis. On careful histologic study a small fibrous scar in the testis with or without remnants of a choriocarcinoma or adult teratoma is demonstrated. This combination has now been observed so often that we must accept that a primary choriocarcinoma of the testis may mature and obliterate itself after metastases have occurred.

Taken together, these four observations indicate that maturation in malignant trophoblastic tumors of the testis does occur. It is possible that with planned research, we might learn what factors are involved and control them to the point of changing a malignant tumor and its metastases into a benign tumor or a mass of fibrous tissue.

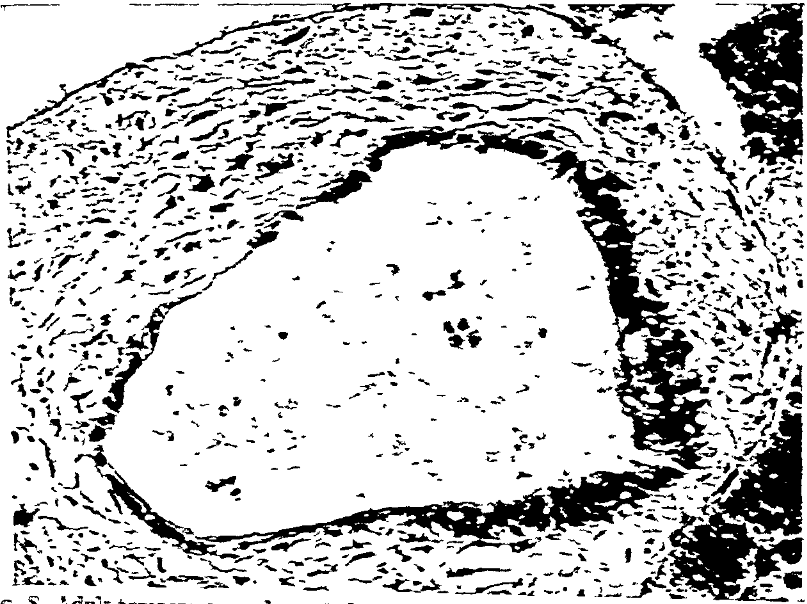

FIG. 8. Adult teratomatous elements in a sinus of the pampiniform plexus of the cord

EMBRYOID STRUCTURES

In a small, but significant number of testicular tumors, especially those containing immature somatic elements, there are distinctive structures which resemble the early stages of the human embryo.

In two dimensions these structures are round or oval (fig. 9). The surrounding compact cellular connective tissue forms a pseudocapsule. Within the structure there are three elements embedded in a loose primitive mesenchyme. The first of these elements is a cystic space lined with a flat cell which fuses with the mesenchyme. The second is a focal collection of cyto- and syncytiotrophoblasts, usually associated with necrosis and hemorrhage. The third is an epithelial acinus of small or moderate size. At one point the epithelium is distinctly taller than in the remaining circumference.

The first of the elements is Häuser's membrane, the second is the placenta, and the third is the amnion and embryo.

called tridermal metastases. Unless we assume that benign adult tissues may metastasize, the explanation of this phenomenon is that malignant cells metastasize and then differentiate into benign cells. An extension of this thinking is that most if not all teratoid tumors are malignant at their inception; some remain so, while others become benign, sometimes before and sometimes after they metastasize.

INDUCTION AND ORGANIZATION IN TROPHOBLASTIC ELEMENTS

In contrast with the somatic elements which are usually benign, the trophoblastic elements in teratoid tumors of the testis are uniformly malignant.

It is generally accepted that benign tumors may transform into malignant, but the reverse, the differentiation of malignant cells into benign cells, is believed to occur only rarely. The best known examples of the latter process are the evolution of neuroblastomas of the adrenal into ganglioneuromas.

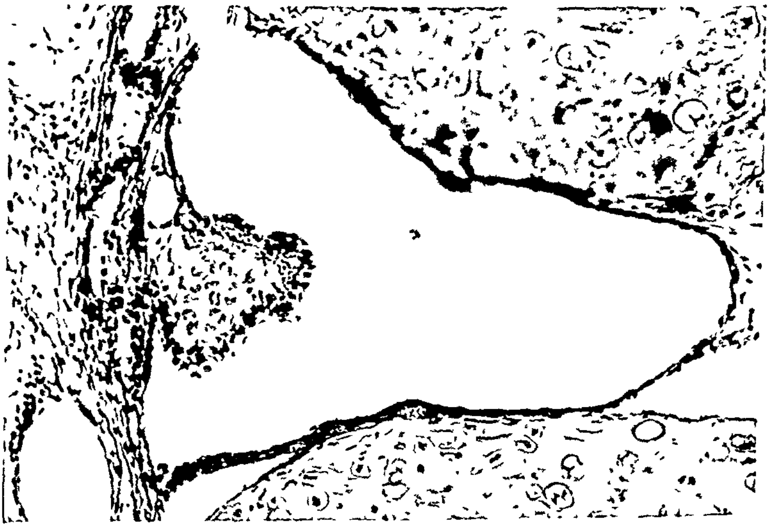

FIG. 7. Joint space between two masses of cartilage in an adult teratoma

The very fact that the process occurs at all gives us some basis for hope that we might learn how to induce it at will.

What evidence is there that maturation may occur spontaneously in the malignant trophoblastic tumors of the testis? I believe there are 4 separate observations to support the view that it does occur.

First, in some choriocarcinomas the orientation between the cyto- and syncytiotrophoblasts is not irregular, but approaches the pattern of a chorionic villus.

Second, as has been pointed out earlier in this paper, many embryonal carcinomas show partial maturation with the formation of early syncytiotrophoblasts (fig. 3, *B*).

Third, in 1 case of choriocarcinoma in this series, comparison of the syncytiotrophoblasts in the primary tumor and in the metastases in the lung 4 months later showed maturation of these cells in about the same degree they would have been expected to mature in four months in a normal placenta.

5) Structures similar to human embryos are observed in a few teratoid tumors. Thus there are many similarities of teratoid tumors and normal embryonic development. A scheme based on this premise has been developed (fig. 10).

In normal development there is fertilization, formation of totipotential cells, division of these into somatic and trophoblastic types, and maturation of the former into a new organism and of the latter into the placenta which is shed at the end of gestation.

For teratoid tumors it is postulated that parthenogenesis of a sex cell forms a group of totipotential cells which also divide into somatic and trophoblastic types. If the somatic development is primary an immature and then mature teratoma is formed. Rare somatic carcinoma and sarcomas originate in teratomas. If the trophoblastic development is dominant there is successively an embryonal carcinoma and a choriocarcinoma. If both elements participate there is the tumor usually designated teratocarcinoma, a combination of both.

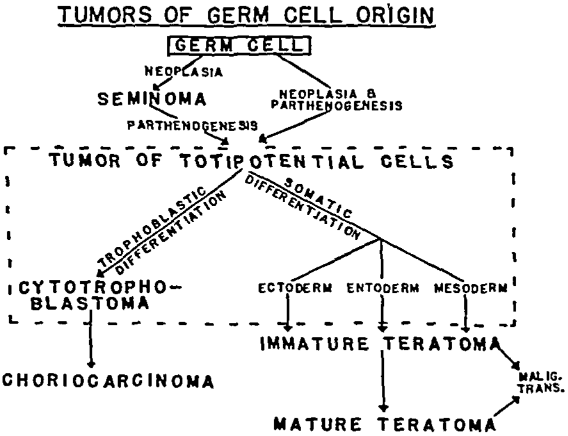

FIG. 10. Scheme of origin and interrelation of teratoid tumors of testis and normal embryonic development.

The seminoma, on the basis of incidence, belongs to the preceding group, but is a little apart from the other members. Hence, I have assumed that the seminoma is a direct neoplastic proliferation of the sex cell. However, in order to account for certain combinations I have further assumed that the neoplastic cell may undergo the equivalent of parthenogenesis and form trophoblastic elements.

It must remain for the future to determine whether this theory is correct or not. It is brought forward purely as a theory and as a basis of future study.

THE FUTURE

A research program is never finished. For each question answered, two new questions arise out of the one answer.

The ultimate, but not necessarily the immediate aim of medical research, is better health care—the prevention and the cure of disease.

As I see the problem of testicular tumor there is need of more basic research: tissue culture studies of cellular types, the relation of cellular type to secretion

The close similarity of these structures with early human embryos justifies the conclusion that they are in fact embryos in the teratoid tumors. This in turn leads to the conclusion that many, if not all, teratoid tumors are derived from a totipotential cell and that parthenogenesis occurs.

A theory of parthenogenetic origin of teratoid tumors would explain the occurrence of tumors of somatic or trophoblastic or all elements, and would explain the known cellular types in complex tumors.

THE NATURE OF TERATOID TUMORS

From time to time it is desirable in scientific work to gather together the known facts and conclusions in order to determine if there is some common pattern. Thus a theory may be proposed not as the final work, but as a framework on which future research can be planned and placed. If these subsequent investigations disprove the theory, then a new theory must be evolved to proceed further.

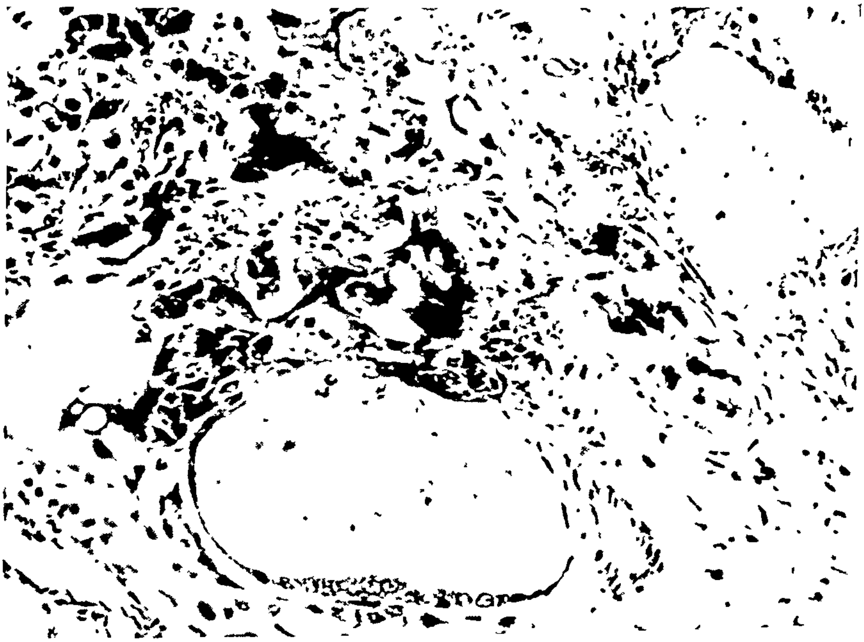

FIG. 9 Embryoid structure in a teratoid tumor

Our studies so far, I believe, fall into a pattern, and a theory of the origin and nature of teratoid tumors is possible. The facts and conclusions are briefly these.

1) There are four basic cellular types of teratoid tumors.

2) The cellular types occur singly and together in definite combinations suggesting an interrelation.

3) Some cellular types are associated with secretion of chorionic gonadotropin and others are not.

4) Induction and organization occur in both the somatic and trophoblastic elements.

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A FEMINIZING ADRENAL TUMOR IN AN ADULT MALE

HENRY MORTENSEN AND (by invitation) LEONARD MURPHY

From the Department of Urology, St. Vincent's Hospital, Melbourne, Australia

The patient K. S. was a well built man of 38 years of age, married with 3 children aged 12, 7 and 3. Nine years previously he had suffered from mild lead poisoning of short duration. His past history and family history were otherwise unimportant. For years he had been a heavy beer drinker.

The patient, when seen in 1949, presented with gynecomastia. The left breast had begun to enlarge 18 months previously, followed rapidly by the right organ. Breast development had been progressive for 12 months since when their size was unaltered. No secretion had occurred. The patient stated that his breasts became tender during his wife's menstrual periods and that he had suffered from morning nausea and vomiting during his wife's pregnancies though she herself was well.

The patient's second symptom was a pain in the right hip felt deep in the joint, causing a slight limp and unaffected by rest or exertion. This had been complained of for a year, at first intermittent but daily and almost constant of late, and radiating at times to the loin. Loss of libido had been present for a year.

He had noticed no loss of weight or diminution in strength or energy.

On examination, he was of normal masculine physique without adiposity. The breasts and nipples were well developed, corresponding to those of a young adult woman (fig. 1). No secretion could be obtained on attempted expression. The hair distribution was that of a male but comparatively sparse and atrophic in the male pubic area. The penis was tapering and rather smaller than one would expect in a man of his build. The testes were small, soft and atrophic; testicular sensation was normal. The prostate was normal.

On examination of the right hip, there was some limitation of external rotation, other movements being normal.

Hemoglobin and plasma protein estimation and blood counts were normal. Rather low serum sodium values were found, three estimations being 288, 320 and 319 mg./100 cc; two values of the chlorides were 480 and 468 mg./100 cc. The fasting blood sugar estimation was 106 mg. and after 50 gm. of glucose, readings of 110, 83, 85 and 92 mg. were obtained at half hourly intervals. The blood chemistry was otherwise normal as was the renal function. The Aschheim-Zondek test was negative.

Estimation of the 17-ketosteroids showed an excretion of 7.6 mg. in 24 hours.

Biopsy of the breasts was not done and testicular biopsy was unsuccessful as a result of defective fixing agents and was not repeated.

Radiological examinations of the pituitary fossa and chest were negative. Excretory urography showed normally situated and normally functioning kidneys.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 26, 1950.

of gonadotropin, histochemical studies of cellular types to define more accurately the cell of origin, and histologic and chemical investigations of induction and organization in tumors.

On the practical side, we should think about, if not work on, that approach to the treatment of tumors which is in its infancy but offers great promise, chemotherapy. If a rare tumor such as a choriocarcinoma undergoes maturation and fibrosis spontaneously, we should be able to isolate chemical substances that induce this change. It is the same change that occurs in the development of every fetus in utero.

Perhaps in between teaching, committee meetings, discussions in the dean's office, and conferences in Washington, I shall be able to contribute in some small measure to further progress, and live to see the day when the development of a testicular tumor does not mean death for 1 of every 2 young men so afflicted.

was induced with pentothal and continued with cyclopropane by controlled respiration. Curare was administered. An incision was made along the length of the tenth right rib which was resected subperiosteally. The pleural cavity was opened through the bed of the rib, the lung elevated and the diaphragm divided. The peritoneum was opened and the tumor felt above the kidney. No evidence of metastases was found in the liver. The peritoneum was then closed and the tumor exposed by extraperitoneal dissection. The exposure was excel-

FIG. 3

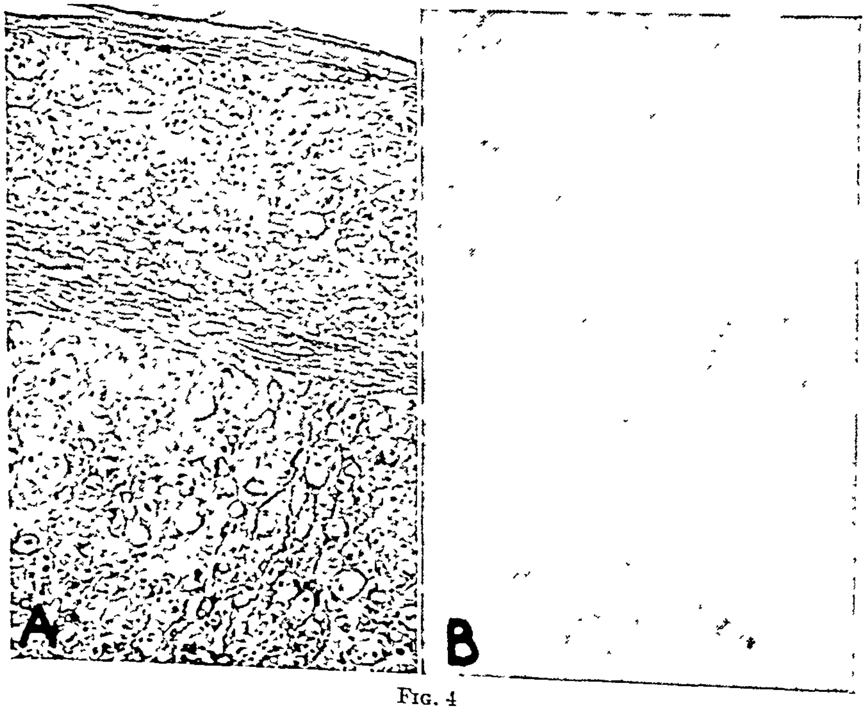

FIG. 4

Perirenal insufflation of air revealed on the left side an adrenal gland of normal shape, size and density (fig. 2). The shadow thrown by the right adrenal, while not increased in surface area, was oval and of a density suggesting a rounded tumor.

It is believed that at this stage the diagnosis of adrenal tumor was not fully proved. Against this, were the normal 17-ketosteroid excretion (the significance of which will be discussed later), the fact that in every case collected by Armstrong and Simpson in 1948 a palpable abdominal tumor was present and the many cases of gynecomastia in the recent literature due to hepatic insufficiency, malnutrition, or belonging to the Klinefelter-Reifenstein-Albright syndrome.

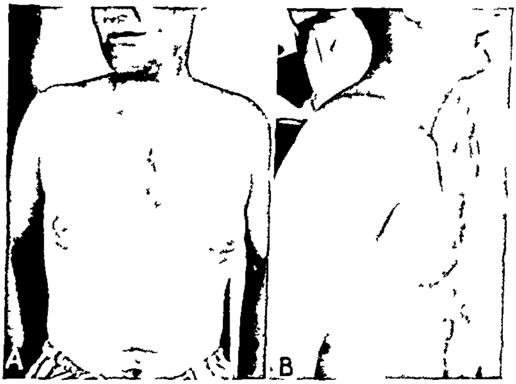

FIG. 1

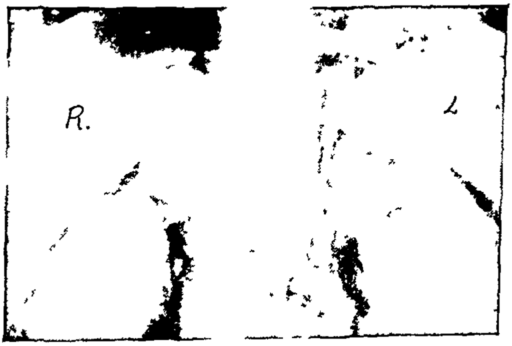

FIG. 2

It was possible to explain the pain in the right hip by the presence of a bony spur on the upper aspect of the acetabulum revealed by x-ray.

The x-rays were sent to Dr. George Cahill of New York for his opinion. The effect of an implant of 100 mg. perandren was tried in the intervening period with resulting return of libido but no alteration in the size of the breasts. The implant was expelled after 3 weeks.

In the next 3 weeks the breasts became painful, the pain in the right loin became much more severe and the patient began to lose weight and it was decided to remove the right adrenal gland. A positive diagnosis of tumor was strengthened by Dr. Cahill's opinion.

Transthoracic removal of a right adrenal tumor was performed. Anesthesia was induced with pentothal and continued with cyclopropane by controlled respiration. Curare was administered. An incision was made along the length of the tenth right rib which was resected subperiosteally. The pleural cavity was opened through the bed of the rib, the lung elevated and the diaphragm divided. The peritoneum was opened and the tumor felt above the kidney. No evidence of metastases was found in the liver. The peritoneum was then closed and the tumor exposed by extraperitoneal dissection. The exposure was excel-

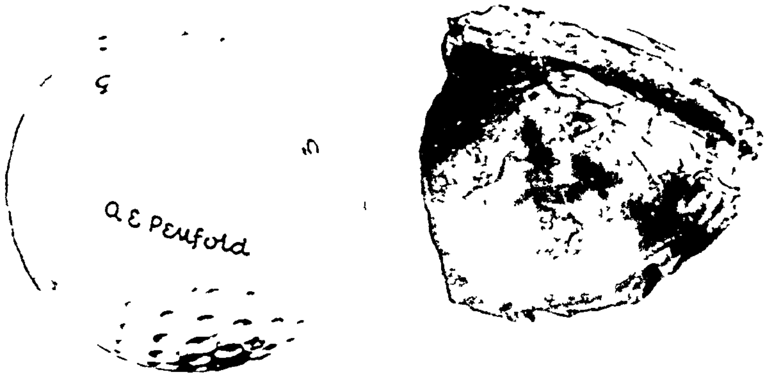

FIG. 3

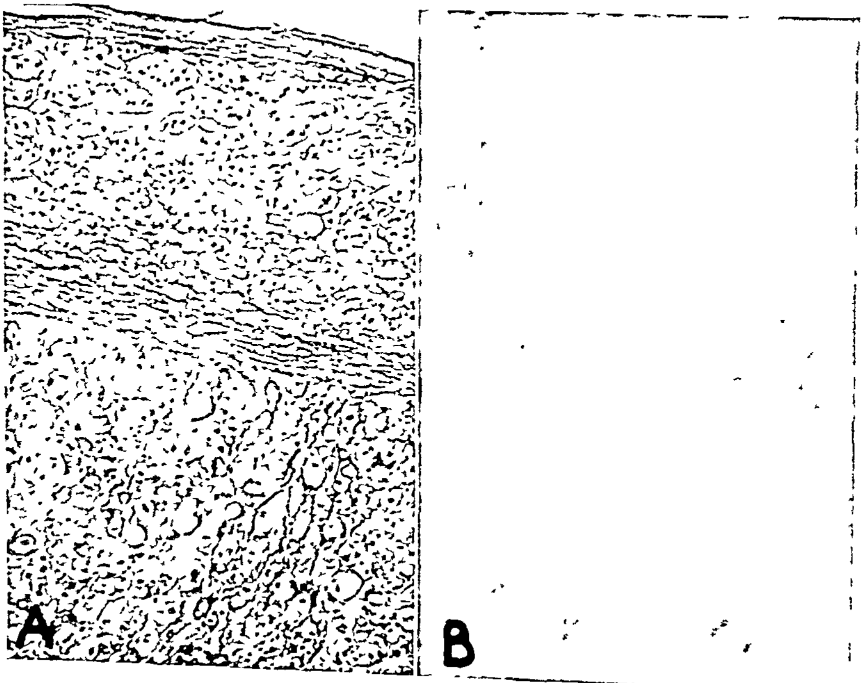

FIG. 4

lent, the many small short vessels being easily secured. The adrenal was removed and its bed packed with oxycel.

The postoperative course gave little anxiety. No adrenal shock occurred. Mild pyrexia was present for 48 hours. A small hydrothorax was aspirated on the fourth day and a persistent intercostal pain abolished by injection of the affected nerve with novocaine.

On macroscopic examination the tumor was globular, slightly smaller than a golf ball and encapsulated. It appeared to distend the gland and had a ridge of normal adrenal tissue around its circumference (fig. 3).

The cut surface appeared homogeneous, yellowish in color and presented a well defined capsule.

"Microscopically the tumor is apparently encapsulated and in the section there is a narrow rim of adrenal tissue covering one portion (fig. 4, *A*). The cells vary somewhat in size and appearance, some being clear like cortical cells whereas others show protoplasm which stains more deeply with eosin (fig. 4, *B*). There are large cells closely set and in places tesselated. There is very little intervening stroma. Nuclei are well stained, some are larger and some stain more deeply than others. In some cells there are two or three nuclei. The findings are those usually described with either masculinising, demasculinising or feminising tumors." (Dr. Andrew Brenan.)

Within 10 days of operation, the patient noticed a decrease in size of the breasts, which was continuing 10 weeks after operation. His libido has returned and his sexual performance he reports as being "perhaps a little too good."

He has no symptoms referable to his incision, his weight is increasing and he presents no evidence of metastases.

DISCUSSION

Thirteen cases of adrenal carcinomas causing a feminizing syndrome in the male have been previously reported in the literature.

The first case was reported by Bittorf in 1919, 5 cases in the next 20 years, and 8 cases since 1939. It is extraordinary that such a striking syndrome has been recognized and investigated so recently.

The average age of the 14 patients was 32 years. Twelve were aged between 26 and 44 years, and the two exceptions were 15 and 5 years old, this last, Wilkins' case, being the only one occurring before puberty.

Gynecomastia was the only feature common to all cases and it was always prominent. Holl observed abnormal pigmentation of the nipples in his 2 cases, the breasts have elaborated a secretion, milky in the case of Zum Busch and watery in Lisser's case. Depression of libido was noted in the only cases (7) in which remark was made on sexual adjustment. Soft, atrophic testes were present in 7 cases. Loss or thinning of the hair of male distribution was present in 5 cases and suggested in 2 others.

Two patients became obese during their illness but in none was a feminine distribution of adipose tissue developed. Holl's patient returned to normal weight after successful removal of tumor.

Pain in the upper abdomen, loin or scapular region has been present in the majority of cases.

Most cases have been well advanced when first seen. Armstrong and Simpson collected 8 cases in 1948, in all of which a palpable abdominal tumor was present and only one of these was successfully operated upon and apparently free of metastases 12 months later.

The two most recently reported tumors have been the smallest; in Wilkins' case, the neoplasm was 3 cm. in diameter, approximately the same size as the tumor here reported.

Lisser's case is of interest in that at autopsy, the adrenal and kidney were separable from the tumor which apparently arose in a retroperitoneal adrenal rest.

Hormonal studies have been made in 6 cases. A minor rise in androgen excretion was noted in the 2 cases in which estimation was done (Simpson and Holl; Roholm and Teilum). In the same 2 cases, in both of which the patients died, gross increase in estrogen excretion was found. However, in the also unsuccessful case of Scott, there was no rise in urinary estrogens and a similar finding was made in Wilkins' surviving case. These tests thus do not appear to be of great help in diagnosis.

17-ketosteroid estimations are available in 4 cases. In Scott's case, the high value of 195.6 mg. daily was found prior to operation, and of this 70 mg. was in the form of dehydroisoandrosterone. After removal of the tumor, the 17-ketosteroid excretion fell to 9.6 mg., the alpha ketosteroid predominating; there were no 17-ketosteroids on analysis of the tumor. In the case of Armstrong and Simpson, with a palpable tumor, 17-ketosteroid excretion was 34 mg. and 4 months later 108 mg. In Wilkins' successful case, 4 mg. 17-ketosteroids was considered slightly greater than normal for a boy of 5 years and in my case, 7.6 mg. was a normal value.

In virilizing tumors in the female, 17-ketosteroid and dehydroisoandrosterone estimations and the color tests are of considerable value in diagnosis. In the four feminizing tumors detailed above, significant findings have occurred only in cases beyond surgical help.

The high degree of malignancy of these tumors is shown by the few long term survivors. In 6 cases the patients died of metastases without surgery, 2 were found to be inoperable at laparotomy. Two cases in which the primary tumor was removed died soon of recurrences. Four cases have survived excision of the tumor and been free of metastases at the time of the report namely at 6 weeks (McFadzean), 6 months (Holl, case 2), 4 years (Wilkins), and 3 months* in my case.

All 4 so far successful cases have shown regression of breast development and return of libido.

SUMMARY

The fourteenth reported case of feminizing tumor of the adrenal in the male is here presented.

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* The patient has since been reviewed 5 months postoperatively and is symptom free.

The ease of approach to the adrenal through a thoraco-diaphragmatic incision is demonstrated.

This is the fourth case recorded surviving excision of such a tumor and free from metastases at the time of report.

REFERENCES

Armstrong, C. N. and Simpson, J.: Adrenal feminism due to carcinoma of adrenal cortex. Brit. Med. J., No. 4555, 782, 1948.

Bittorf, A.: Nebennierentumor and Geschlechtsdrusenausfall beim Manne. Berl. klin. Wehnschr., **56:** 776, 1919.

Holl, G.: Zwei mannliche Falle von Nebennierenindentumoren mit innersekretorischen Storunge. Deutsch. Ztschr. f. Chir., **226:** 227–295, 1930.

Lisser, H.: A case of adrenal cortical tumor in an adult male causing gynecomastia and lactation. Endocrinology, **20:** 567–569, 1936.

McFadzean, A. J. S.: Feminization associated with carcinoma of adrenal cortex. Lancet, **2:** 940, 1946.

Pico Estrada, O.: Efectos feminizantes de los tumores suprarenals en el hombre. Rev. med. de Rosario, **30:** 807–819, 1940.

Roholm, K. and Teilum, G.: Feminizing tumors of suprarenal cortex with description of a case. Acta Med. Scandinav, **3:** 190, 1942.

Scott, W. W.: Quoted by Wilkins, L.

Simpson, S. L. and Joll, C. A.: Feminization in a male adult with carcinoma of adrenal cortex. Endocrinol., **22:** 595, 1938.

Wilkins, L.: Feminizing adrenal tumor causing gynecomastia in a boy of 5 years. J. Clin. Endocrinol., **8:** 111, 1948.

Zum Busch, J. P.: Gynakomastie bei hypernephrom. Deutsche med. Wschnschr., **55:** 323, 1927.

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ABNORMALITIES OF THE KIDNEYS, URETERS, AND PERINEPHRIC FASCIA: ANATOMIC AND CLINICAL STUDY

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The perinephric fascia which embeds the kidneys and ureters, first described by Gerota in 1895,[1] has received considerable attention and study. However, relationships between changes in this fascia and prenatal and postnatal abnormalities in the kidneys and ureters have received relatively little attention clinically. In a study of the continuity of this fascia within the abdomen and pelvis, as demonstrated by the dissections and air insufflation, Tobin and Benjamin[2] described 1 case in which there appeared to be some relation between fascial changes and anomalies of the ureters and kidneys. Furthermore Tobin[3] demonstrated in a newborn that the fascia was absent from the same side on which there was agenesis of kidney and ureter.

A survey of the rather extensive literature dealing with anomalies of the genito-urinary tract, beginning with the classic studies of Ballowitz,[4] has revealed no direct comment regarding the probable significance of perinephric fascial changes in association with abnormalities of the ureters and kidneys. A suggestion of such an interrelationship appears in a statement by Anson and coworkers[5] to the effect that "The connective tissue organ capsules function like fascia, separating adjacent structures and apparently of greater significance in the mechanics of embryonic development than has hitherto been appreciated." Our previous observations on the anatomy and clinical significance of fascial layers[2, 3] suggested a study of the peri-ureteral fascial-like bands associated with abnormalities of the perinephric fascia, ureters, and kidneys. This study deals with 22 cases, 16 of which were surgically explored and the remaining 6 were studied at the time of postmortem examination. For convenience, these cases are classified and discussed, with some modifications, according to the plan of Smith and Orkin.[6]

This study was supported with funds from the Dr. Henry C. Buswell Memorial.

Read at annual meeting, American Urological Association, Washington, D. C., June 1, 1950.

[1] Gerota, D.: Beiträge zur Kenntnis des Befestigungsapparates der Niere. Arch. f. Anat. u. Entwickl., Anat. Abteil., **19**: 262-285, 1895.

[2] Tobin, C. E. and Benjamin, J. A.: Continuity of the fasciae lining the abdomen, pelvis and spermatic cord. Surg., Gynec. & Obst., **83**: 575-596, 1946.

[3] Tobin, C. E.: The renal fascia and its relation to the transversalis fascia. Anat. Rec., **89**: 295-311, 1944.

[4] Ballowitz, E.: Ueber angebornen einseitigen, Vollkommen Nierenmongel. Virchow's Arch. f. path. Anat., **141**: 309-390, 1895.

[5] Anson, B. J., Pick, J. W. and Cauldwell, E. W.: The anatomy of commoner renal anomalies: ectopic and horseshoe kidneys. J. Urol., **47**: 112-132, 1942.

[6] Smith, E C. and Orkin, L. A.: A clinical and statistical study of 471 congenital anomalies of the kidney and ureter. J. Urol., **53**: 11-26, 1945.

BILATERAL METANEPHRIC AGENESIS

The perinephric fascia could not be found in 2 cases (1M and 1F) of complete metanephric agenesis. The male patient lived 1 hour and 20 minutes after birth while the female was a stillborn. Since bilateral metanephric agenesis is of little clinical significance it will not be considered further because it has been adequately studied by Amolsch,[7] Nation,[8] Potter,[9] and others.

UNILATERAL METANEPHRIC AGENESIS

In 8 cases of unilateral metanephric agenesis (4M and 4F) the fascia could not be found in the retroperitoneal space on that side on which the kidney and ureter were absent. In 2 other cases of unilateral metanephric agenesis the ureter was partially represented and the embedding fascia was thin and delicate, ending with the cephalad tip of the ureter. It is of some interest to note that unilateral metanephric agenesis was found on the left side in 8 (4M and 4F) of the 10 cases. The prevalence of anomalies of the kidneys and ureters on the left side is discussed by Hinman,[10] while the surgical aspects of renal agenesis has been reviewed by Gutierrez.[11]

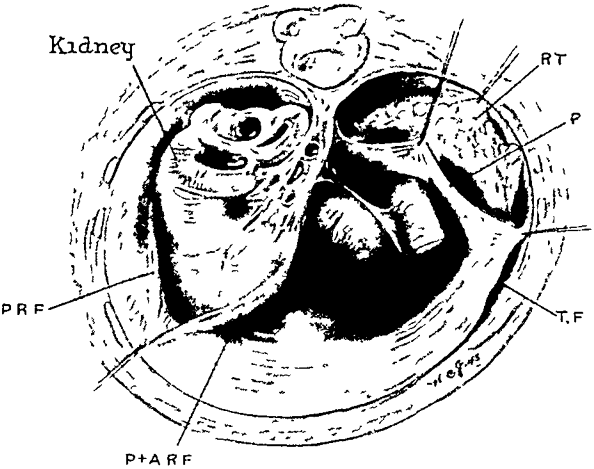

FIG. 1. Cephalic view of cross section from lower abdomen and pelvis of a 2-day old infant with congenital absence of left kidney. No renal fascia or perinephric fat is formed on that side. Retroperitoneal tissue (R.T.) in the region of missing kidney is represented only by a layer of fat and connective tissue. Right kidney is enlarged and pelvic in position. Renal fascia on right side is thin and the anterior layer (A.R.F.) fused with peritoneum (P.), while posterior layer (P.R.F.) is adherent to transversalis fascia (T.F.). (From original by Tobin, fig. 8, Anat. Rec., **89:** 304.)

The following cases with unilateral metanephric agenesis were selected to illustrate fascial changes in association with some abnormalities of the kidney and ureter.

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[7] Amolsch, A. L.: Bilateral metanephric agenesis. J. Urol., **38:** 360–370, 1937.
[8] Nation, E. F.: Renal agenesis. Surg., Gynec. & Obst., **79:** 175–181, 1944.
[9] Potter, E. L.: Bilateral renal agenesis. J. Ped., **29:** 68–76, 1946
[10] Hinman, F.: The Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1935, p. 460.
[11] Gutierrez, R.: Surgical aspects of renal agenesis. Arch. Surg., **27:** 686–735, 1933.

In unilateral renal agenesis it was observed that if the kidney and ureter were absent, the perinephric fascia was also absent (fig. 1); however, on that side on which the kidney and ureter were present, the fascia was also present. On the other hand, any or all of these structures may show variation, and other anomalies may be coexistent. For example, in the case of one patient there was some question as to the factors which might be responsible for the hydronephrosis (fig. 2, *A*) since pregnancy, an aberrant renal artery, and uterus duplex were present. After delivery of a normal baby the hydronephrosis did not change. Surgical exploration revealed an aberrant artery in addition to fascial-like bands at the ureteropelvic juncture and slight nephroptosis. The bands and aberrant artery were surgically released in addition a Kelly-Brödel nephropexy was carried out with partial disappearance of the hydronephrosis (figs. 2, *B* and *C*).

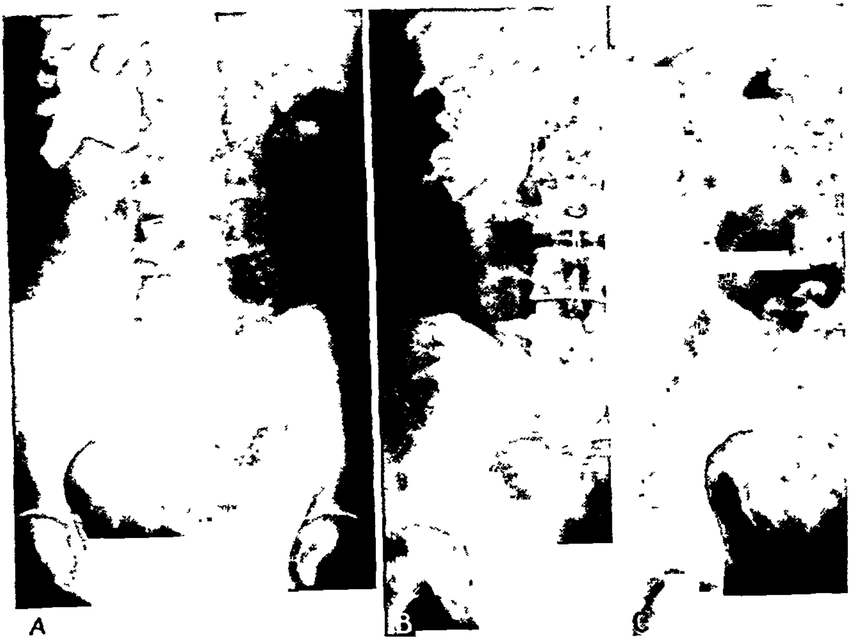


Fig. 2. *A*, retrograde pyelogram shows right and only kidney of a 19-year old 6 months' pregnant woman with ureteropelvic juncture obstruction and hydronephrosis. Surgical exploration revealed bands and an aberrant artery at this site. *B*, retrograde pyelogram taken 3 months postoperatively to show widened ureteropelvic juncture after release of artery and bands. *C*, excretory urogram taken in standing position to show improved drainage. Preoperatively there was almost complete retention of dye.

Another patient was believed to have an aberrant vessel at the ureteropelvic juncture (figs. 3, *A* and *B*) but at the time of surgical exploration there were multiple dense bands at this site similar to those shown by Campbell.[12] These bands were released and a Foley Y ureteroplasty together with a Kelly-Brödel type of nephropexy were carried out with improvement of both renal function and of pyelographic appearance (figs. 3, *C* and *D*). Prior to surgery monthly transfusions were required, but, for some unexplained reason, three transfusions

[12] Campbell, M.: Pediatric Urology. New York: Macmillan Co., 1937, vol. 1, p. 288, fig. 197 (see insert).

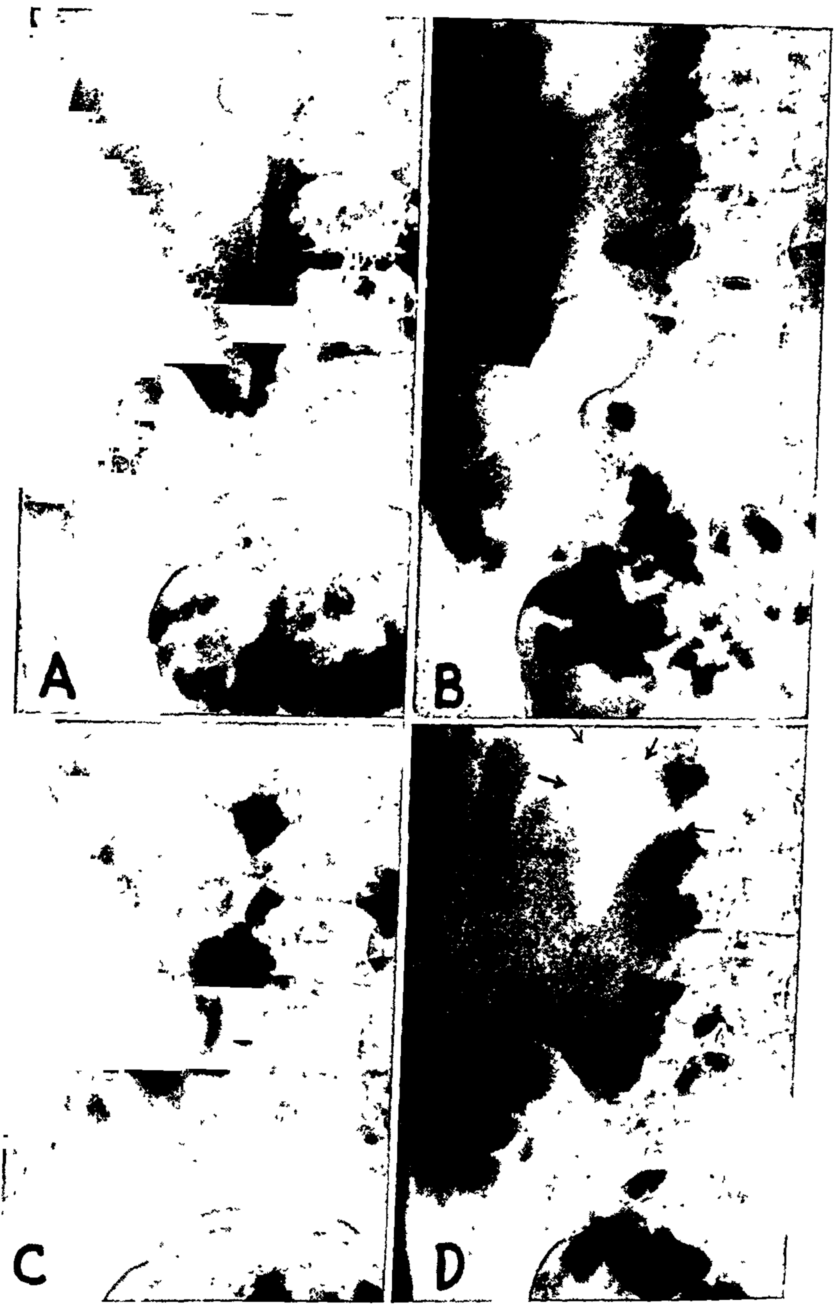


FIG. 3. *A*, right and only kidney of an 11-year old girl with other malformations and aplastic anemia. Retrograde pyelogram shows ureteropelvic juncture obstruction and hydronephrosis *B*, retrograde pyelogram taken preoperatively in standing position demonstrated nephroptosis and poor drainage. *C*, retrograde pyelogram shows widening of ureteropelvic juncture and less hydronephrosis after release of bands and a Foley Y ureteroplasty. *D*, postoperative urogram taken in standing position shows improved position of kidney and better drainage after Kelly-Brödel nephropexy. Pelvis outlined by arrows.

were required for the patient's anemia 1 year after surgery and none the second year.

In some instances the ureter may be quite dilated and tortuous (figs. 4, 5 and 6). In 1 patient (fig. 5, *A*) it was noted that the ureter seemed to be elongated between the fascial-like bands, which appeared to be acting as anatomical points of fixation. Multiple bands were surgically released, and 8 cm. of excessively long ureter was resected obliquely. Then an end-to-end anastomosis was carried out (fig. 5, *B*) according to the methods of Boveé[13] and Hinman[14] over a 10F soft rubber catheter. Fibrosis is shown in the resected ureter (fig. 6, *B*) as compared to a normal ureter (fig. 6, *A*).

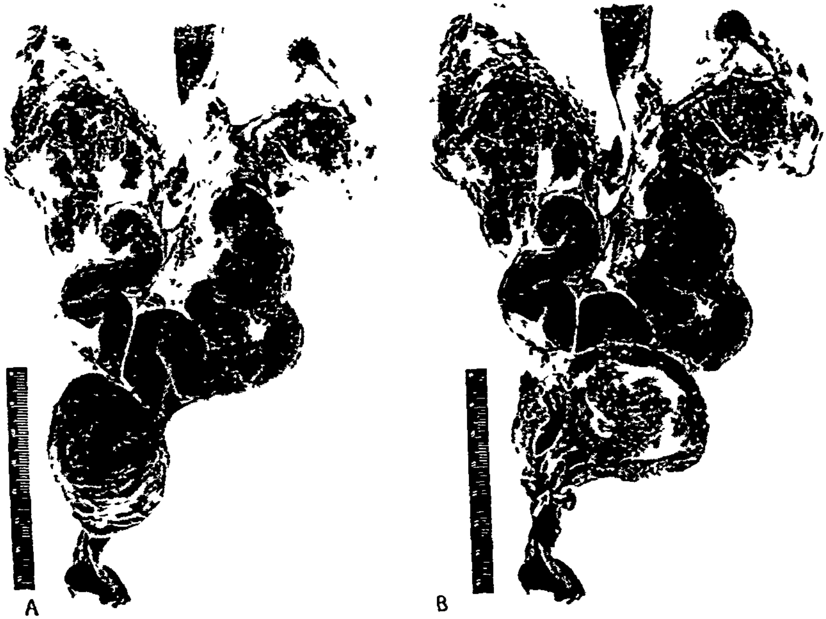


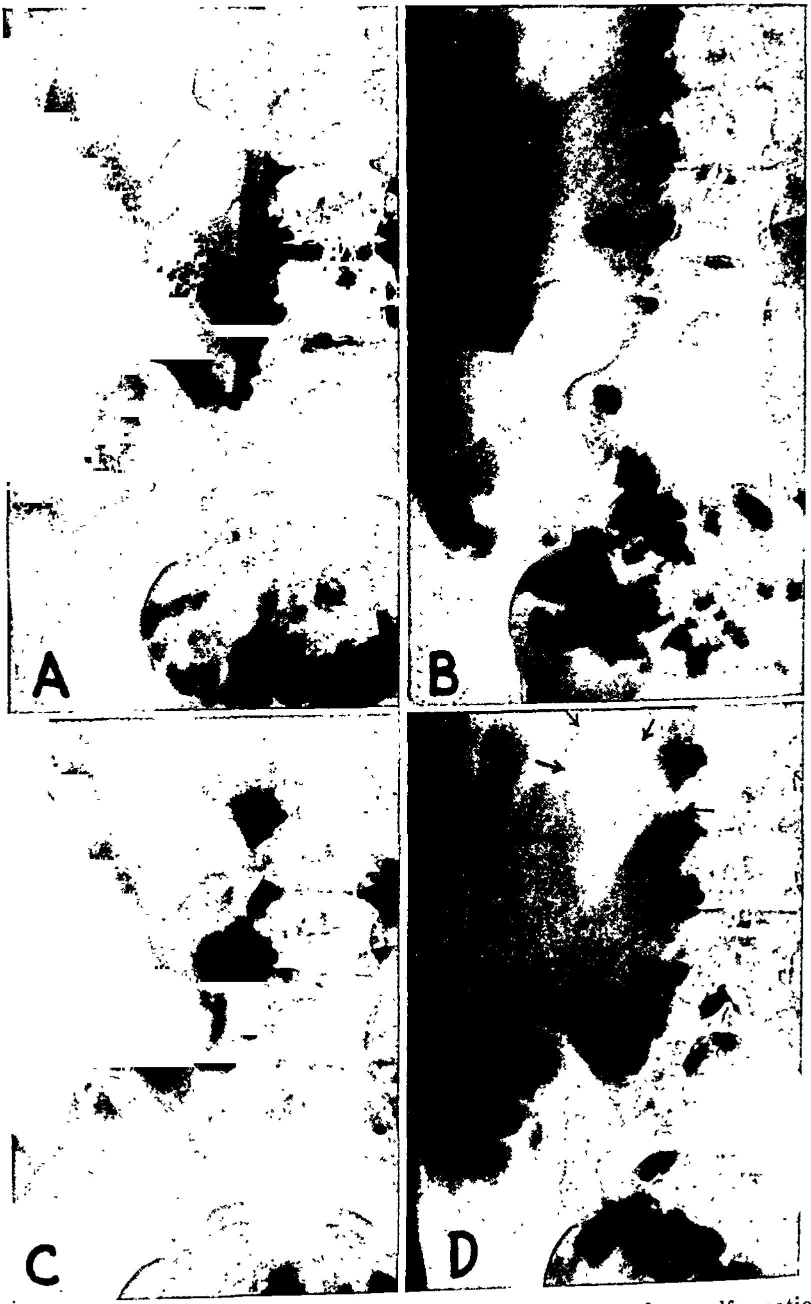
Fig. 4. Postmortem specimen of kidneys, dilated tortuous ureters, bladder, urethra, and aorta from a 3-week old male infant which shows many thick and dense perinephric fascial-like bands about ureters and extending onto bladder anteriorly, *A*. In addition a congenital, prostatic ureteral valve, type 1 (arrow) was found, *B*. Note marked changes in prostatic urethra, bladder, ureters, and kidneys.

In one patient the obstruction was so marked that the renal pelvis and ureter showed marked dilatation (figs. 7, *A* and *B*), and severe parenchymal damage as evidenced by renal clearances and blood chemistry findings. In addition the patient had pathological fractures of both femoral necks. At the time of surgical exploration multiple bands were found along the course of the ureter and appeared to obstruct this structure especially at a point near the bladder (fig. 7, *B*).

As discussed previously, when part of the ureter was present (figs. 8, *A* and

[13] Boveé, J. W.: Uretero-ureteral anastomosis. Ann. Surg., 25: 51–79, 1897.

[14] Hinman, F.: Obstructive hydro-ureteral angularity with hydronephrosis in children. Arch. Surg., 18: 30–62, 1929.



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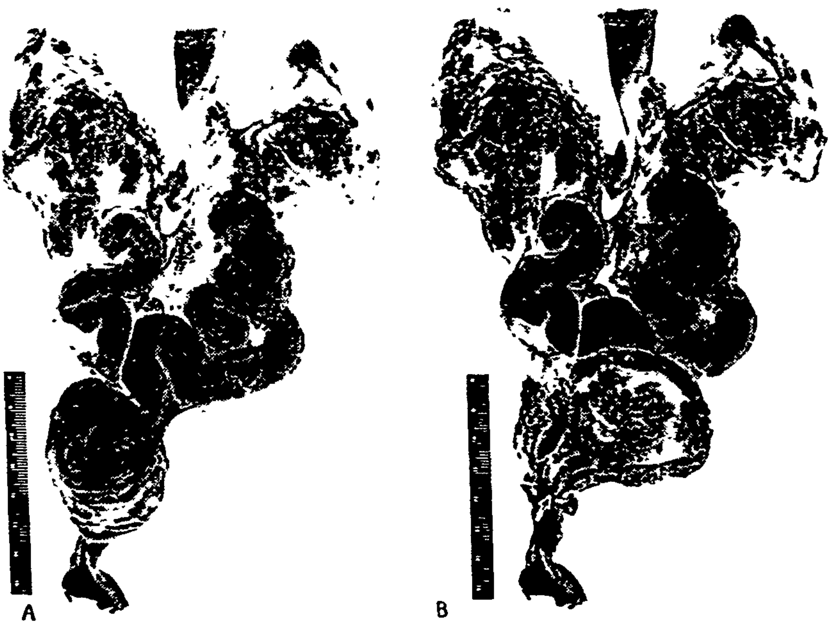

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[14] Hinman, F.: Obstructive hydro-ureteral angularity with hydronephrosis in children. Arch. Surg., 18: 30–62, 1929.

B), then the perinephric fascia was also partially represented. In 2 patients (1M and 1F) having this condition the ureteral stump was surgically explored and removed, and the fascia was found to be thin and delicate. No fascia could be identified beyond the point at which the ureter ended cephalad. As a result of these two observations one might be justified in concluding that the kidney need not be present in order for the fascia embedding the atrophic ureter (fig. 9) to develop to some degree.

The remaining 10 patients (2M and 8F), in whom both kidneys were present, the fascial changes were manifested mainly as band formation. These peri-ureteral fascial-like bands, while not the initiating factors in the production of ureteral obstruction, very likely played some role in the maintenance of this condition. Furthermore these bands may bear some relation to changes in ureteral twisting, elongation, and function.

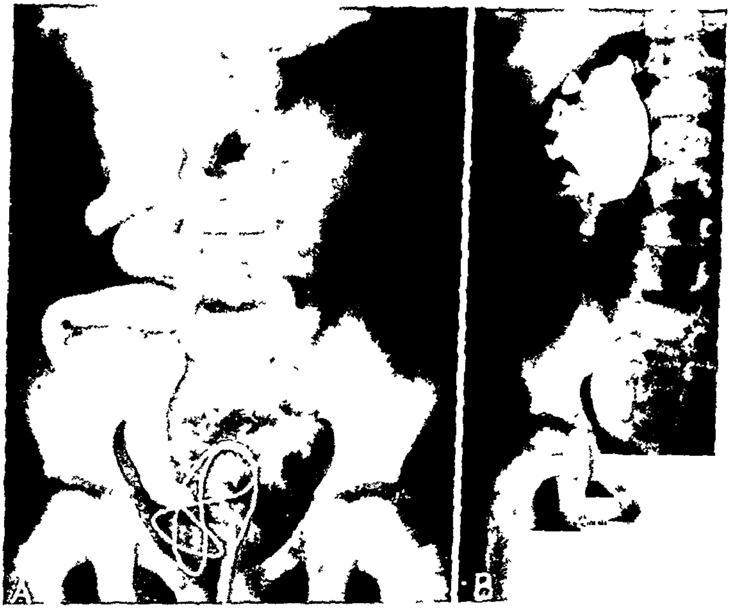

FIG. 5. *A*, right and only kidney of a 6-year old girl with chronic Esch. coli pyelonephritis. Multiple fascial-like bands found along course of ureter were surgically released. (By permission of Surg., Gynec. and Obst.) *B*, pyelo-ureterogram shows result of releasing bands and oblique resection of excessive length of ureter near ureterovesical juncture.

UNILATERAL HYDRONEPHROSIS AND HYDRO-URETER

While 1 case with hypertension, pathological fractures of both tibias, and a mild degree of unilateral hydronephrosis and hydro-ureter did not show much pyelographically (fig. 10, *A*), the blood chemistry and phenolsulfonphthalein clearance indicated considerable change in the function of the right kidney. At the time of surgical exploration multiple bands were found producing obstruction at the ureteropelvic juncture and at different points along the ureter. In addition it was noted that the ureter was elongated and dilated between the firm fascial-like bands. In view of these findings a nephro-ureterectomy was done. Luminal narrowing in branches of the right renal artery (fig. 10, *B*) was an incidental finding to chronic pyelonephritis and both appeared to bear some relationship to his hypertension, because after nephro-ureterectomy the blood pressure was somewhat lowered.

A 5-months old female had complete bilateral duplication of pelves and ureters associated with recurrent severe attacks of Esch. coli pyelonephritis (fig. 11). The retrograde pyelograms showed a marked degree of hydronephrosis of the upper left pelvis and a kinked tortuous hydro-ureter (fig. 12, *A*). Surgical exploration revealed multiple fascial-like bands along the course of both left ureters. After the bands had been released, both ureters were excessively long. Since the function of the upper renal parenchyma was greatly diminished (phenolsulfonphthalein excretion was less than 5 per cent at the end of one-half hour) the upper pelvis with its parenchyma and ureter were completely removed. The lower ureter was then excessively long. A 5 cm. segment was resected obliquely, and end-to-end anastomosis was performed over a 8F soft rubber catheter. The result of the reconstructive surgery is shown in fig. 12, *B*.

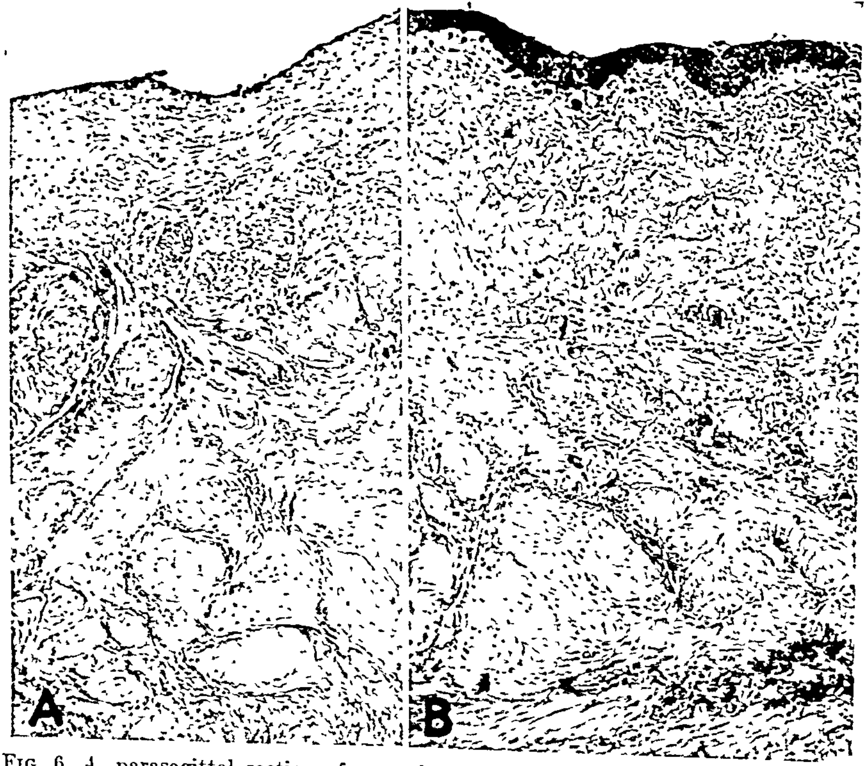

FIG. 6. *A*, parasagittal section of normal ureter. (Hematoxylin and eosin × 60.) *B*, parasagittal section of ureter from this patient to show fibrosis involving various layers. (Hematoxylin and eosin × 60.)

Another patient with hydronephrosis had obstruction produced by fascial-like bands at the ureteropelvic juncture and at the lower ureter, both on the right side (fig. 13, *C*). When these bands were surgically released, the ureter was excessively long but not narrow. Subsequently 3 cm. of the ureter was resected obliquely at the ureteropelvic juncture with anastomosis to the pelvis over a 12F Foley catheter. The results of reconstructive surgery are shown in figures 13, *E* and *F*.

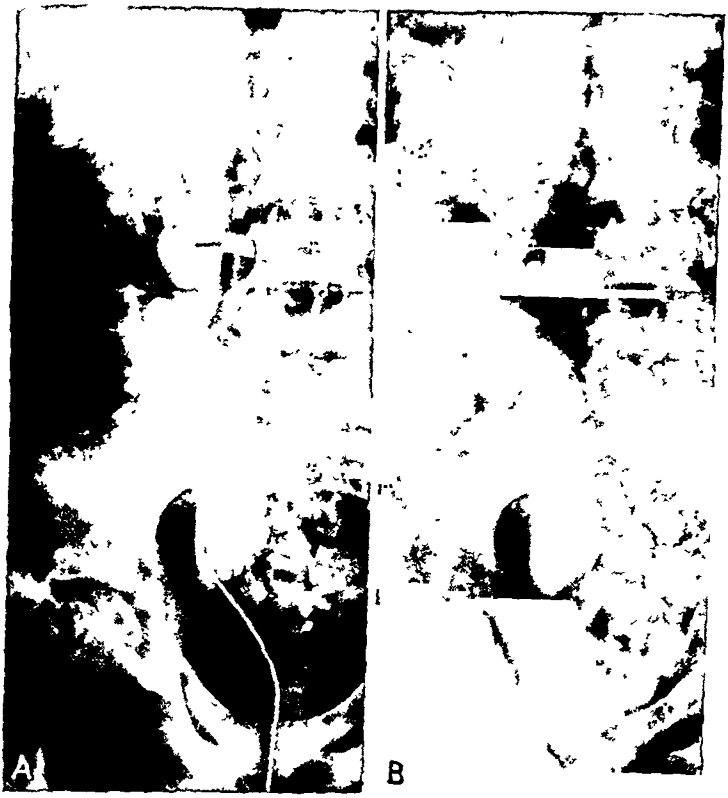

Fig. 7. *A*, retrograde pyelogram shows a marked right hydro-ureter and hydronephrosis involving only ureter and kidney in a 24-year old man with pathological fractures of both femoral necks. *B*, retrograde pyelogram taken in standing position to demonstrate lack of drainage of dye, ureter obstructed at point near bladder.

RENAL RICKETS

In 1 patient with renal rickets (hyperparathyroidism) and hypoplastic left kidney, both retroperitoneal spaces were surgically explored. Fascial-like bands, although thin, were present along the course of the ureter. The bands were not surgically released because of her poor general condition as partly evidenced by the blood chemistry studies which indicated severe uremia.

UNILATERAL INCOMPLETE DIVISION OF THE URETER

Nordmark[15] pointed out that patients with unilateral incomplete division of the ureter are prone to have pain and infection. Two patients with pain and

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[15] Nordmark, B.: Double formation of the pelves of the kidneys and the ureters. Embryology, occurrence, and clinical significance. Acta. radiol., 30: 267–278, 1948

Esch. coli infection who had unilateral incomplete division of the ureter (both upper right) were found to have heavy bands producing some obstruction at the point of juncture of the two ureters. In the first patient the obstruction was so marked that both pelvic components showed marked dilatation and the phenolsulfonphthalein excretion from both right pelves revealed less than a total of 5 per cent in one-half hour. Therefore nephro-ureterectomy was performed. In the second case, the bands were not so dense and the lower right ureter showed marked narrowing at its juncture with the ureter which drained the upper pelvis (fig. 14, *A* and *B*). The bands which rotated the lower ureter posteriorly were released and a side-to-side anastomosis carried out. The result of the procedure is shown in fig. 14, *C* and *D*.

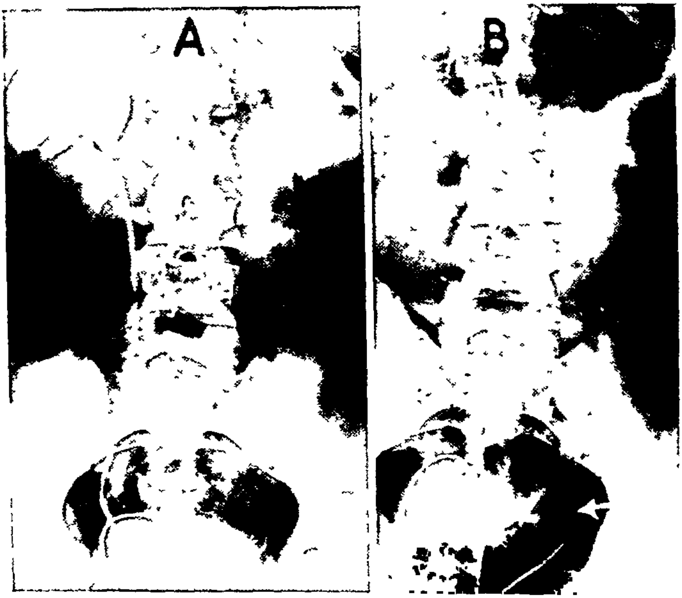

FIG. 8. *A*, retrograde pyelogram shows right and only kidney of a 20-year old man with hypertension and complaining of marked fatigue. *B*, retrograde left ureterogram reveals a remnant of ureter (arrow). At time of cystoscopy, it was observed that left side of trigone and ureteral orifice were atrophic.

ECTOPIC URETER

In 1 patient the left ureter was found to empty into the floor of the urethra near the bladder neck (fig. 15, *A*). At the time of surgery, very dense and tight bands were found next to the urethral wall. These bands were not released, but instead the ureter was cut obliquely caudad to the bands, and implanted into the bladder near the midtrigone where the rate of bladder growth might be less (fig. 15, *B*). Monie[16] suggested that abnormal differences in the rate of growth of the lateral and medial portions of the bladder wall, in some cases of double ureters, may cause anomalous position of the ureteric openings. It is possible that this condition may also be found in cases with one ureter, and may account for changes in the ureter and fascia near the uretero-urethral junction as found in this patient.

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[16] Monie, I. W.: Double ureter in two human embryos. Anat. Rec., **103**: 195–204, 1949.

TRAUMA AND ABERRANT ARTERY

The importance of the perinephric fascia in limiting the spread of extravasates is well demonstrated in figure 16. This 7-year old boy was hit by a passenger bus and came into the Emergency Department in severe shock with a blood pressure of 30/0, and with the right flank progressively enlarging. A 10 minute excretory urogram (despite this very low blood pressure an adequate excretory urogram was obtained) showed the spread of diodrast into the space limited by the perinephric fascia. In this instance the ureter had been completely severed by an aberrant renal artery which was bleeding. Around both the artery and ureter were several fascial-like bands. The artery was ligated, the bands released about the ureter, and the ureteral defect corrected by an end-to-end anastomosis over a 6F whistle-tip catheter.

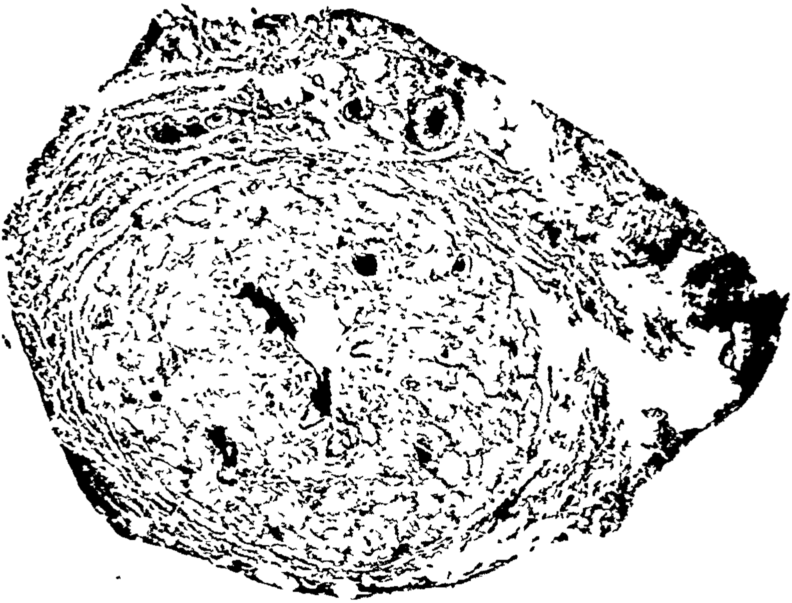

FIG. 9. Cross section of left ureter from same patient as figure 8 to show marked degree of atrophy. (Hematoxylin and eosin × 23.)

VESICO-URETEROPELVIC REFLUX

In another patient cystograms demonstrated left vesico-ureteropelvic reflux and twisting of the ureter (fig. 17, *A*). During surgical exploration of the ureter, several firm fascial-like bands were found at the site of the twisting. These were released and the ureter became straight, longer, and slightly dilated. After implanting the ureter into the midtrigone region of the bladder it was found that the ureter had an excessive length of 2 cm. protruding into the bladder lumen.

This part of the ureter was removed. A postoperative cystogram did not show reflux (fig. 17, *B*), and a postoperative ureterogram showed the ureter to be straight (fig. 17, *C*).

COMPLETE EXSTROPHY OF THE BLADDER

In a 9-month old female with complete exstrophy of the bladder, no abnormality of the perinephric fascia could be found. In this patient, the ureters were partially explored and then implanted into the rectosigmoid using the Coffey 1 technique. Although both ureters were slightly dilated at the ureterovesical juncture, no bands could be identified comparable to those found in the patient with an ectopic ureter, where bands were obstructing the ureter to some degree at the uretero-urethral juncture. Since the ureters entered the exstrophied bladder at considerable angulation it is probable that this condition explains the dilatation of these structures. Later the bladder defect was closed and the changes in the labia were surgically corrected.

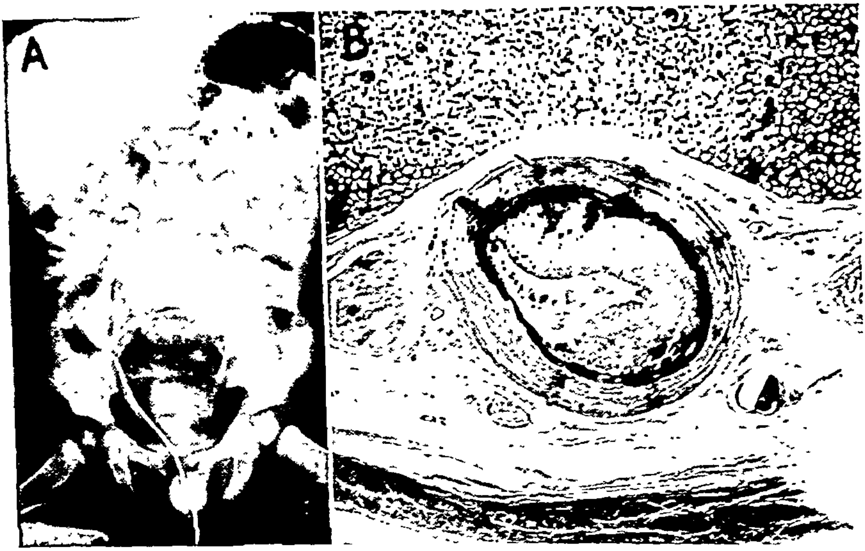

FIG. 10. *A*, retrograde pyelogram shows multiple points of obstruction along right ureter with blunting of calyces. During surgery multiple bands were found along course of ureter. This 2-year old boy also had pathological fractures of both tibias, delayed closure of anterior fontanelle, hypertension, and a question of coarctation of aorta. *B*, narrowing of lumen in a branch of renal artery by proliferation of connective tissue of intimal layer. (Verhoeff elastic tissue stain.)

DISCUSSION

As pointed out by Östling,[17] Davis,[18, 19] and others, intrinsic ureteral lesions may be present and account for ureteral and pelvic dilatation and changes in

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[17] Östling, K.: On the genesis of hydronephrosis particularly with regard to the changes at the uretero-pelvic junction. Acta Chir. Scand., 86: suppl. 72: 122 pages, 1942.

[18] Davis, D. M.: Intubated ureterotomy: Result after four years. J. Urol., 57: 233–237, 1947.

[19] Davis, D. M., Strong, G. H. and Drake, W. M.: Intubated ureterotomy: Experimental work and clinical results. J. Urol., 59: 851–862, 1948.

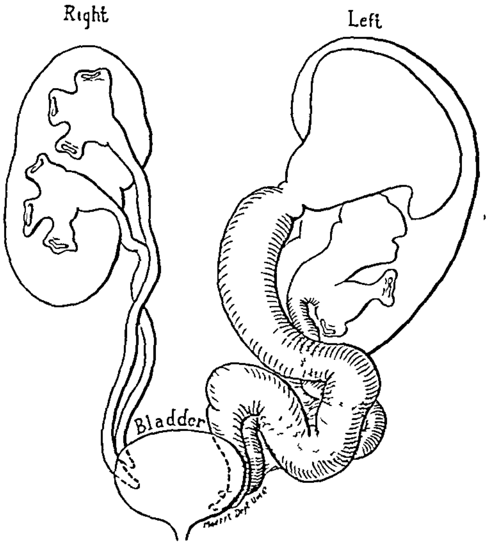

FIG. 11. Drawing to show bilateral complete duplication of ureters and pelves in a 5-month old female with a history of chills, fever, and abdominal distention.

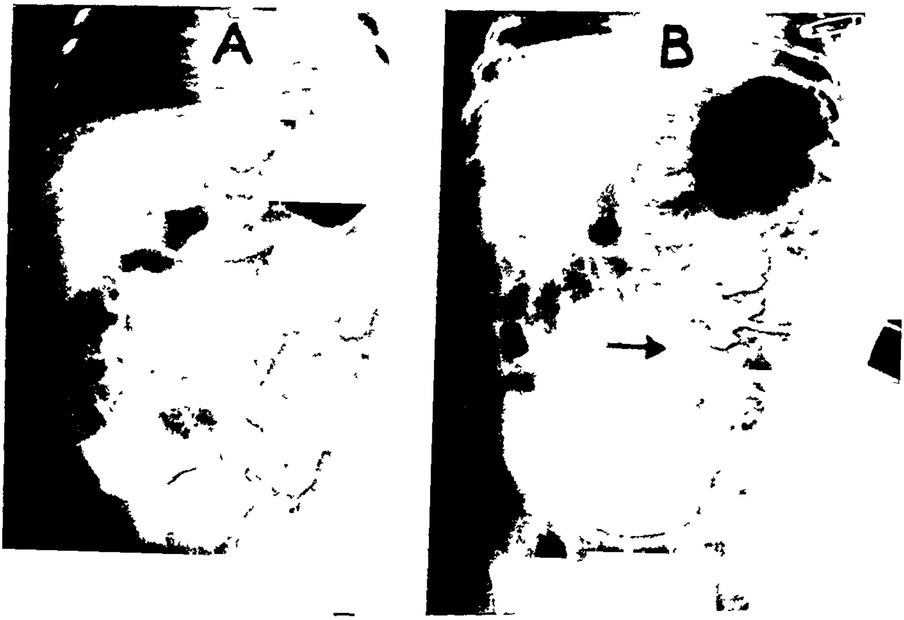

FIG. 12. *A*, retrograde pyelogram showing marked degree of hydronephrosis of upper left pelvis and a tortuous kinked hydro-ureter, produced in part by multiple fascial-like bands. *B*, after surgical release of multiple fascial-like bands and removal of upper pelvis and its ureter, lower ureter was excessively long. Pyelo-ureterogram 15 days after surgery shows result of oblique resection of 5 cm. of ureter, end-to-end anastomosis over a 8F soft rubber catheter, nephrostomy, and a Kelly-Brodel nephropexy. (Arrow points to site of ureteral anastomosis.)

the renal parenchyma. At times, according to Irvin and Kraus,[20] hydronephrosis is quite evident and yet no definite obstruction can be demonstrated in the

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[20] Irvin, G. E. and Kraus, J. E. Congenital megaloureter and hydroureter. Arch. Path., 45: 752-765, 1948.

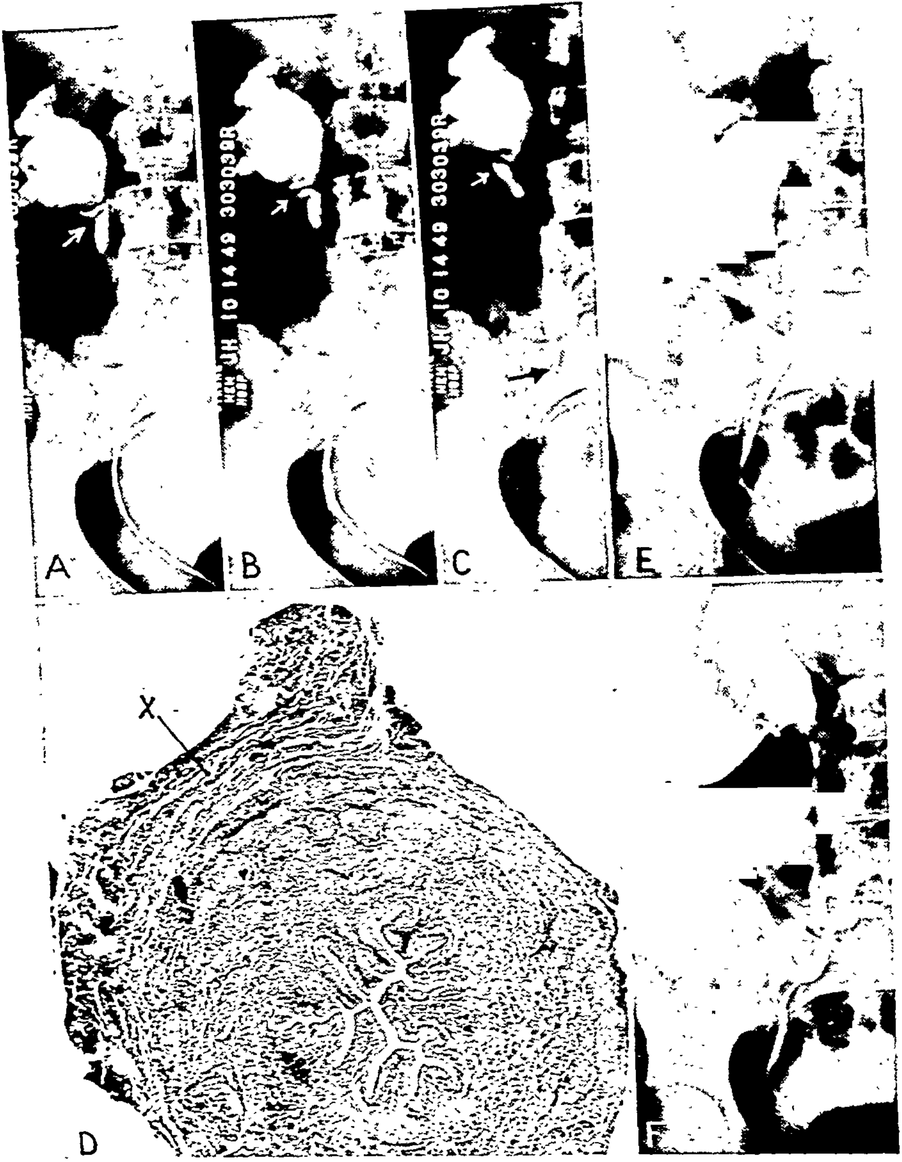

FIG. 13. *A*, *B*, *C*, retrograde serial pyelograms show right hydronephrosis with obstruction at ureteropelvic juncture in a 35-year old female suffering from right flank pain and Esch. coli infection. Note at ureteropelvic juncture, that upper kink (above arrow in *A* and level with arrow in *B*) is constant in all three exposures (*A*, *B*, and *C*), while lower kink in *A* (level with arrow) disappeared in *C* (marked by arrow). In addition, lower ureter is partially obstructed (black arrow). Fascial bands were formed at both sites. *D*, part of a fascial-like band (*X*) is shown adherent to ureteral wall. This specimen is from site marked by white arrow in *B*. (Hematoxylin and eosin.) *E*, ureterogram shows result of surgical release of bands about lower ureter. Compare with site of lower arrow in *C*. *F*, pyeloureterogram taken 16 days after surgery shows result of oblique resection of 3 cm. of ureter at ureteropelvic juncture, end-to-end anastomosis over a 12F Foley catheter, nephrostomy and Kelly-Brödel nephropexy.

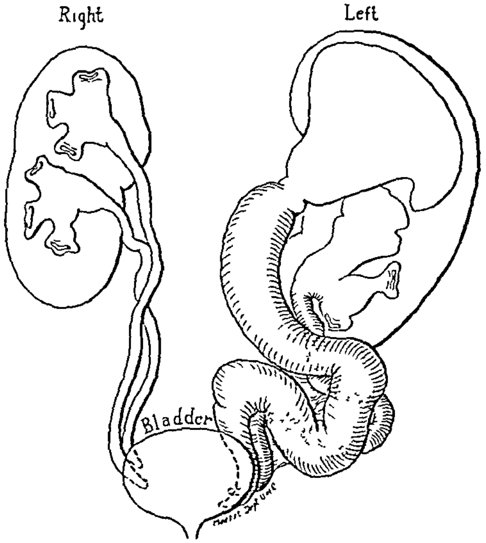

FIG. 11. Drawing to show bilateral complete duplication of ureters and pelves in a 5-month old female with a history of chills, fever, and abdominal distention.

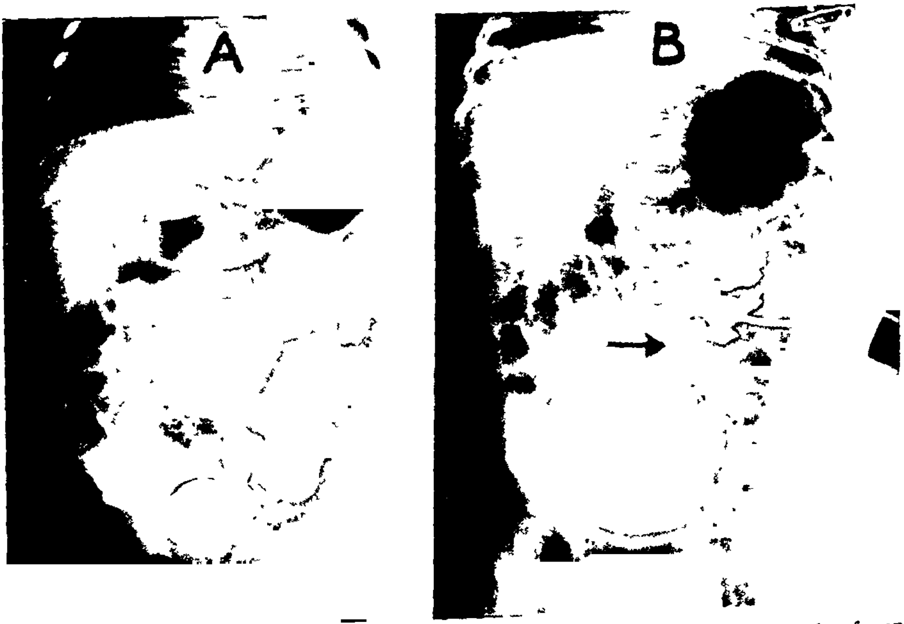

FIG. 12. *A*, retrograde pyelogram showing marked degree of hydronephrosis of upper left pelvis and a tortuous kinked hydro-ureter, produced in part by multiple fascial-like bands. *B*, after surgical release of multiple fascial-like bands and removal of upper pelvis and its ureter, lower ureter was excessively long. Pyelo-ureterogram 15 days after surgery shows result of oblique resection of 5 cm. of ureter, end-to-end anastomosis over a 8F soft rubber catheter, nephrostomy, and a Kelly-Brodel nephropexy. (Arrow points to site of ureteral anastomosis.)

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[20] Irvin, G. E. and Kraus, J. E.: Congenital megaloureter and hydroureter. Arch. Path., 45: 752–765, 1948.

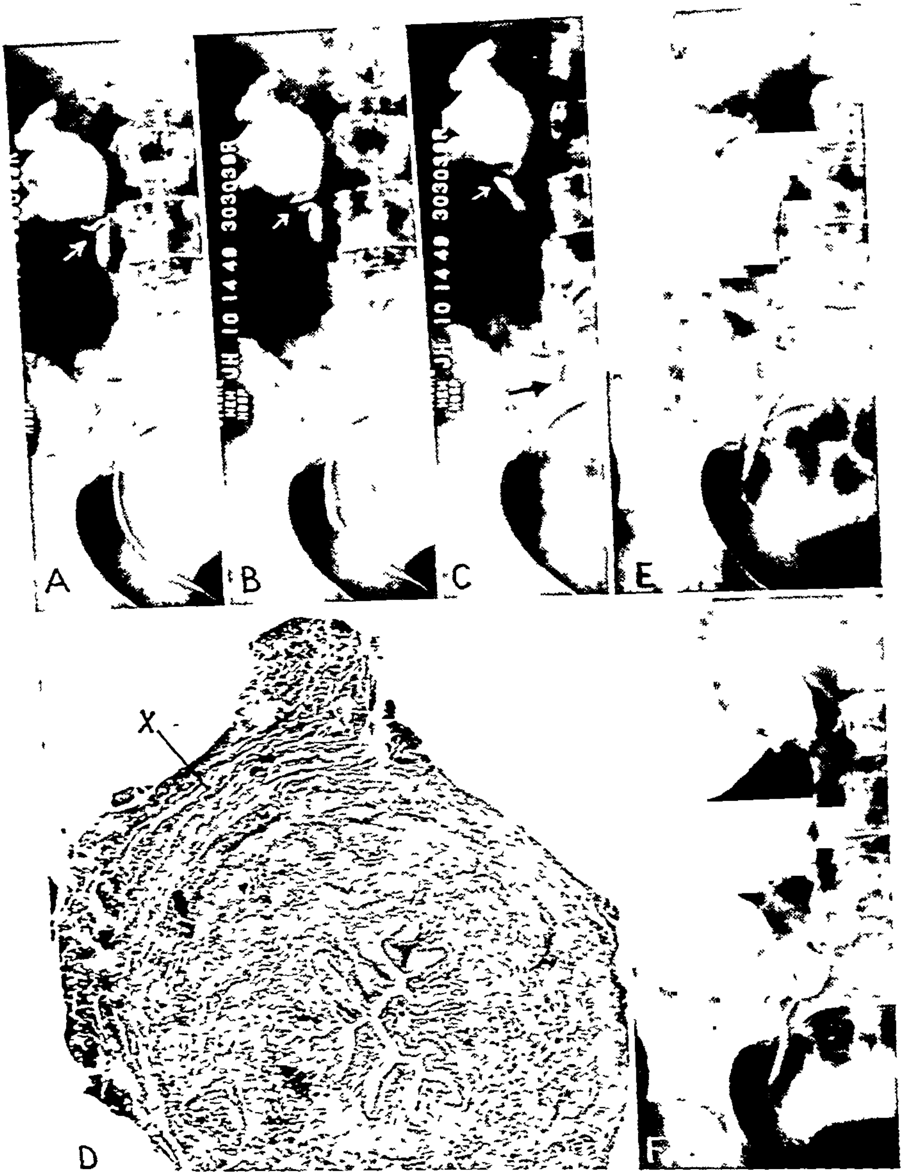

FIG. 13. *A*, *B*, *C*, retrograde serial pyelograms show right hydronephrosis with obstruction at ureteropelvic juncture in a 35-year old female suffering from right flank pain and Esch. coli infection Note at ureteropelvic juncture, that upper kink (above arrow in *A* and level with arrow in *B*) is constant in all three exposures (*A*, *B*, and *C*), while lower kink in *A* (level with arrow) disappeared in *C* (marked by arrow). In addition, lower ureter is partially obstructed (black arrow). Fascial bands were formed at both sites. *D*, part of a fascial-like band (X) is shown adherent to ureteral wall. This specimen is from site marked by white arrow in *B*. (Hematoxylin and eosin.) *E*, ureterogram shows result of surgical release of bands about lower ureter. Compare with site of lower arrow in *C*. *F*, pyeloureterogram taken 16 days after surgery shows result of oblique resection of 3 cm of ureter at ureteropelvic juncture, end-to-end anastomosis over a 12F Foley catheter, nephrostomy and Kelly-Brödel nephropexy.

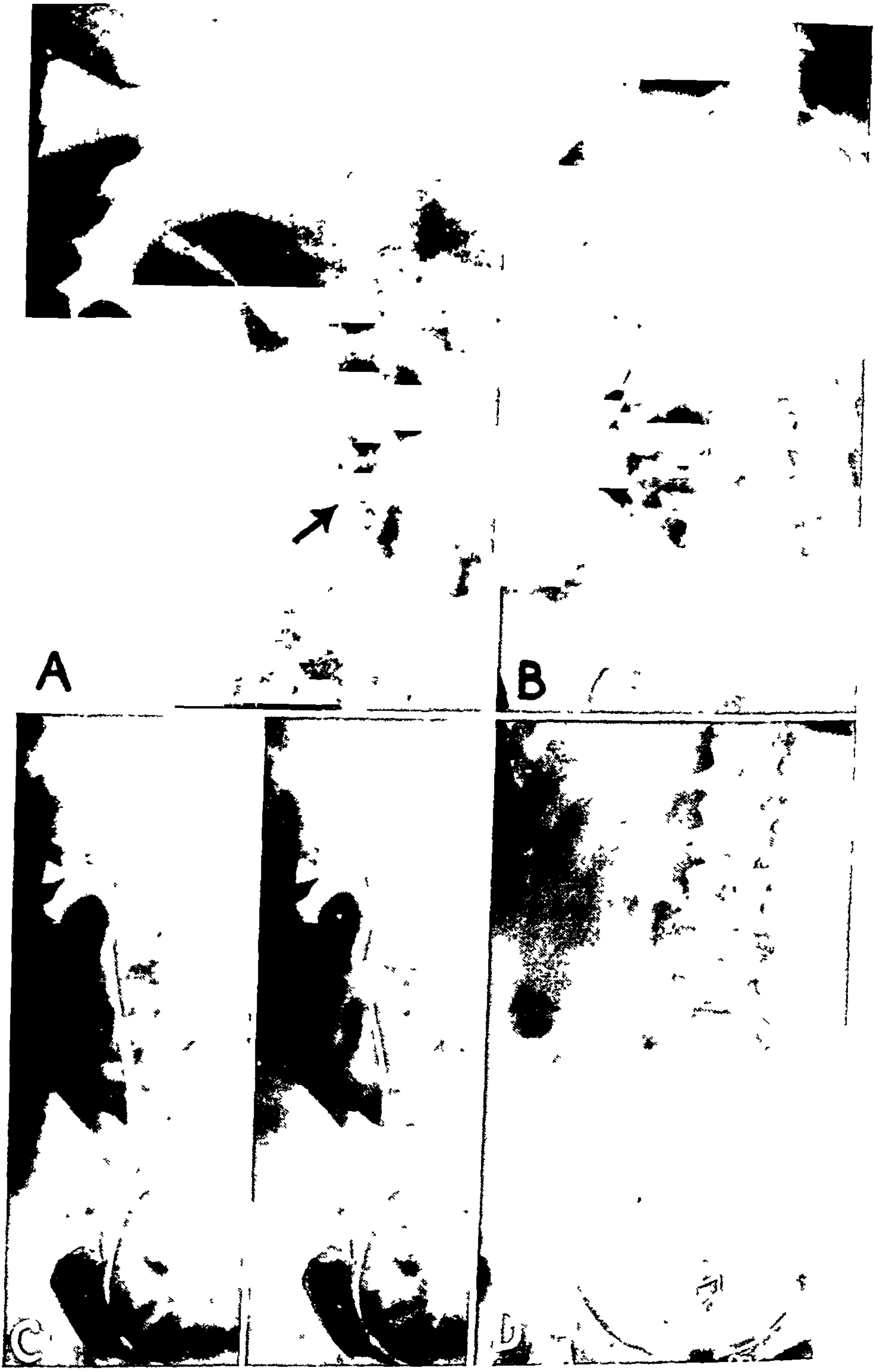

FIG 14. *A*, preoperative retrograde pyelogram enlarged to demonstrate more clearly narrowness of lower right ureter as it joined upper one (arrow) Patient, a 25 year old nurse, had right flank pain and recurrent attacks of Esch coli infection *B*, preoperative retrograde pyelogram taken in upright position to show poor drainage of lower right pelvis *C*, postoperative retrograde pyelograms to show result of side-to-side anastomosis of upper two ureters after bands had been released about their juncture. Lower ureter was rotated posteriorly by these bands *D*, postoperative excretory pyelogram taken in upright position to demonstrate adequate drainage of both right pelves

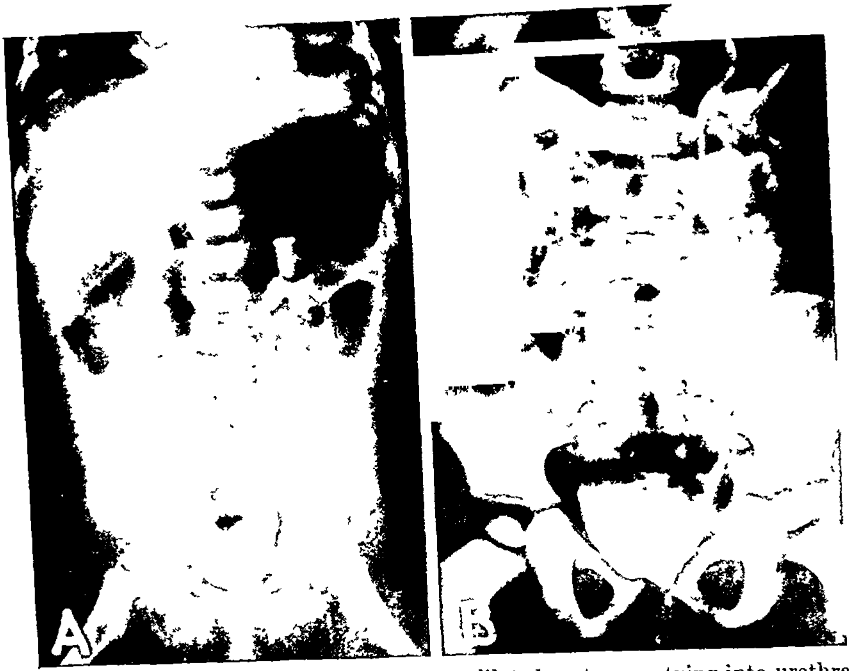

FIG. 15. *A*, retrograde pyelogram shows left dilated ureter emptying into urethra in a 4-month old female who had recurrent attacks of chills, fever, and Esch. coli infection. *B*, note changes in ureter and pelvis 16 months after transplantation of ureter into mid-trigone region of bladder.

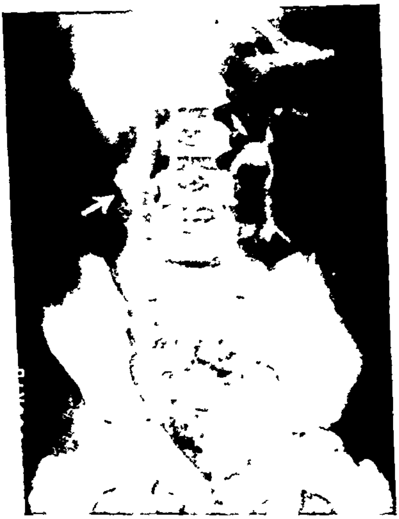

FIG. 16. A 10 minute excretory urogram of a 7-year old boy revealed extravasation of diodrast into right perinephric space, periphery of which was limited by perinephric fascia. During cystoscopy it was observed that right ureteral orifice was not functioning (note bladder defect). Since he sustained a fracture of bony pelvis it is possible a hematoma was formed which may have put pressure against right side of bladder. Furthermore, rectal examination revealed a right rectal mass. (By permission of Surg., Gynec. and Obst.)

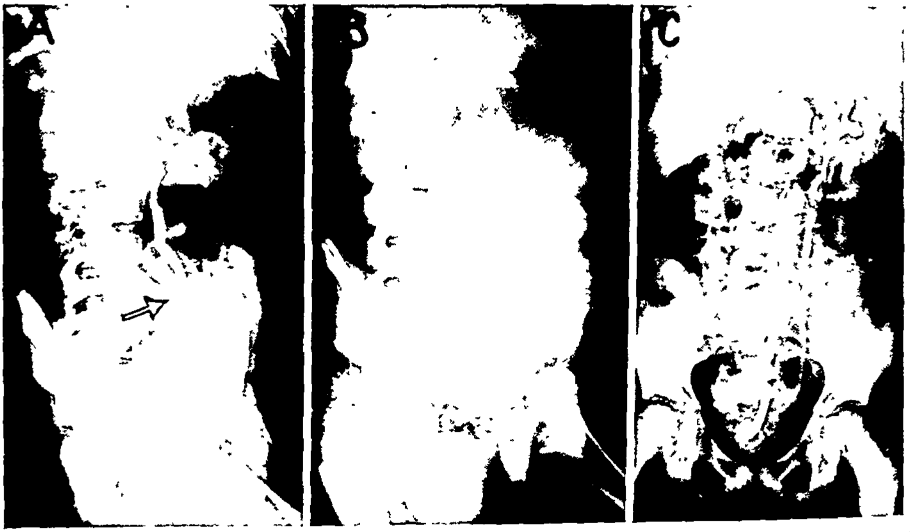

Fig. 17. *A*, cystogram (5 per cent skiodan) to show left vesico-ureteropelvic reflux in a 4-year old female who had recurrent attacks of Esch. coli infection. Lateral view to show twist in ureter (arrow). *B*, postoperative cystogram, lateral view, shows absence of reflux. *C*, pyelo-ureterogram taken 16 days after surgery to show straight ureter and absence of twisting.

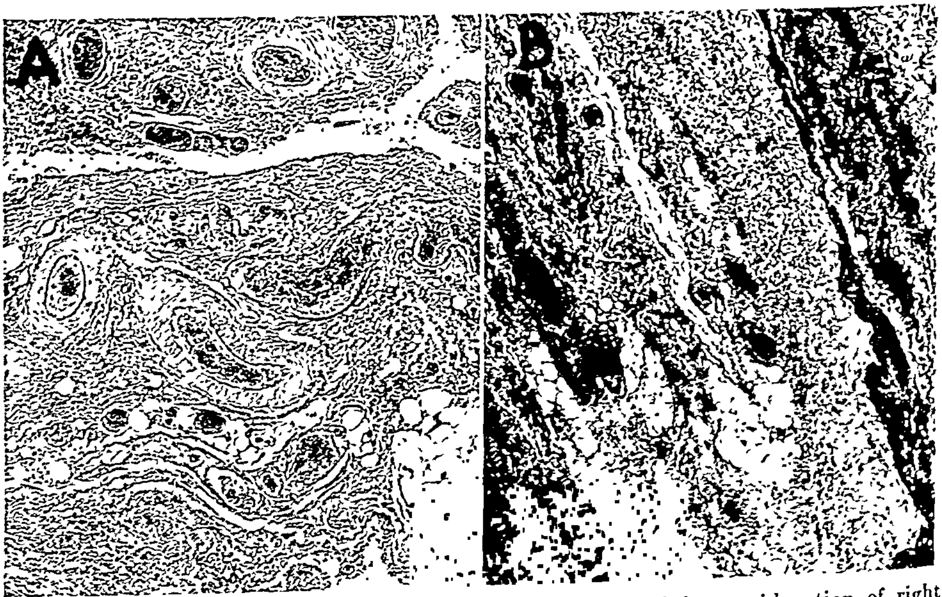

Fig. 18. Photomicrographs of a fascial-like band removed from midportion of right ureter in a 4-year old boy. Patient had marked bilateral ureteral obstruction and hydronephrosis with multiple bands along course of both ureters. *A*, section showing many vessels within band. (Hematoxylin and eosin × 60.) *B*, adjacent section which shows dense collagenous bands (dark areas) as demonstrated by Mallory connective tissue stain (× 60).

ureter or at the ureteropelvic juncture. Duncan and Goodwin[21] placed a band of cellophane around either one or both ureters of dogs without actually constricting the ureteral wall itself. The tissue reaction to the cellophane was one of sclerosis with increasing fibrosis to such a degree that the ureter was constricted. As a result of this reaction obstruction was produced and hydro-ureter with hydronephrosis developed. Henriksen[22] found in his study of the lymphatic spread of carcinoma from the cervix and body of the uterus that ureteral obstruction was evident in 82.8 per cent of the nontreated cases and 78.6 per cent of the treated cases. Everett, et al.[23] reached similar conclusions from their studies on the effect of radiation therapy, for carcinoma of the cervix, upon the urinary tract. Furthermore, inflammatory reactions may develop to such a degree that the ureter will be obstructed, as was seen in the case presented by Heymann and Martin.[24]

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[21] Duncan, G. W. and Goodwin, W. E.: Experimental urinary tract obstruction produced by cellophane sclerosis. Surg., 25: 113–116, 1949.

Finally perinephric or peri-ureteral fascial-like bands may also be associated with ureteral obstruction as was pointed out in this paper. It becomes clear, indeed, that a number of conditions might involve the ureter to produce obstruction.

Furthermore it appears that these fascial-like bands may be formed in some cases by condensations of the fascia (figs. 13, *D* and 18, *A* and *B*) which act as points of anatomical fixation. As a result, the ureter may become elongated, tortuous, and twisted between these bands. Along with this ureteral obstruction, changes in the tissue of the ureteral wall itself may occur (fig. 6, *B*). This may explain, to some degree, ureteral atony found in such cases. After release of these fascial-like bands, in most cases, it was necessary to correct other ureteral changes, such as excessive length or narrowing of the wall itself, by suitable reconstructive surgical procedures.

SUMMARY

Perinephric fascia changes and peri-ureteral fascial-like bands were found in association with certain abnormalities of the kidneys and ureters.

The perinephric fascia could not be identified, and apparently did not develop, when bilateral renal agenesis existed.

In unilateral renal agenesis, the perinephric fascia could not be identified in the retroperitoneal space in which the ureter and kidney were absent.

If the ureter were partially represented, the fascia was poorly developed and ended with the cephalad tip of the ureter.

In most patients, after the release of these bands it was necessary to correct excessive ureteral length or narrowing by suitable reconstructive surgical procedures.

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[22] Henriksen, E.: The lymphatic spread of carcinoma of the cervix and the body of the uterus. Am. J. Obst. & Gynec., 58: 924–942, 1949.

[23] Everett, H. S., Brack, C. B. and Farber, G. J.: Further studies on the effect of irradiation therapy for carcinoma of the cervix upon the urinary tract. Am. J. Obst. & Gynec., 58: 908–923, 1949.

[24] Heymann, W. and Martin, J. F.: Bilateral megalo-ureter in a child. J. Ped., 35: 618–624, 1949.

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Printed in U.S.A.

DISCUSSION

DR. CHARLES MONTGOMERY STEWART (Los Angeles, Calif.): Dr. Benjamin's paper is a concise summation of those causes of ureteral and renal obstruction which have been misinterpreted or completely ignored. The slides demonstrating his postoperative results are conclusive, visible proof of the soundness of his preoperative contentions. Attempts to add to a paper as complete as Dr. Benjamin's could only result in a repetition of facts already recorded.

Dr. Donald Charnock first interested me in this problem at the Childrens Hospital in Los Angeles several years ago. Marked ureteral dilatation, especially in children, progresses through two distinct phases. The first phase results from obstruction at, or distal to, the ureterovesical junctions. This dilatation is one of increase in ureteral diameter only. At this stage, removal of the obstruction usually results in regression of ureteral dilatation, completely or in part. Complete regression may not occur, but at least progression of the dilatation is halted.

The second phase begins when a maximum increase in ureteral diameter has been reached, and greater ureteral capacity can only be obtained by a gradual increase in ureteral length. In increasing its length, the ureter now must adapt itself to a space which has a degree of limitation somewhat resistant to this enlargement. This limitation to expansion in the retroperitoneal space does not in itself cause obstruction. Limitation of free mobility occurs along the lengthened ureter at anchor points provided by the peri-ureteral fascial bands, and it is at these points where the ureter now begins to obstruct itself. The greatly elongating ureter is forced to actually twist and kink with resultant flexion compression at the points where these fixed fascial bands are present. Once the second phase has been reached, regression not only does not occur after the removal of the primary cause of obstruction, but dilatation has been observed to progress. This progressive dilatation in the second phase is solely due to the ureter actually obstructing itself at the peri-ureteral fascial anchor points. On surgical exploration of these ureters which have progressed through the two phases of dilatation, it has been observed that peristalsis was present and active. Manual compression of these ureters before they were mobilized did not result in ready emptying of the contained urine into the bladder. However, following the removal of the restricting peri-ureteral fascial bands and complete mobilization of the ureter, manual compression of the ureter readily emptied the contained urine into the bladder. We do not hesitate to resect 10 to 14 cm. of these elongated ureters. End to end anastomoses have given good postoperative results from a drainage standpoint, and in those cases where the second phase of obstruction was evident, progressive ureteral and renal obstructive damage has been arrested.

Delayed cystograms have proven to be a valuable diagnostic aid in many instances where incompetence of the ureterovesical junction could not be determined in any other way. When concentrated contrast medium is instilled into the urinary bladder, and retained continuously while x-ray exposures are taken at variable intervals during the following one to three hours, the resulting films have been named "delayed cystograms."

Dr. Abraham G. Fleischman (Des Moines, Iowa): We owe Dr. Benjamin and his associates our personal felicitations for re-emphasizing the importance of the perinephric fascia, and for again directing our attention to the reconstructive surgery and the management of increased ureteral length.

I have been extremely interested in that particular phase of the subject because, in the early thirties, when many of us were interested in doing renal sympathectomies and adrenal denervations and presacral neurectomies, we were told by many investigators that we would have subsequent disturbance in the innervation of those organs, but experience has indicated that such is not the case. In the instances where I have resected redundant, tortuous ureters, the improvement in the renal function sometimes has been remarkable, which indicates the remarkable recuperative power of the kidney when the drainage is ample.

I am sure that those of you who have viewed the exhibit of Dr. Lewis' new concept of the megalo-ureter were impressed with the fact that previously we have not managed correctly this particular pathological condition. We must not forget that frequently the condition is associated with marked hydronephrotic kidneys, and unless that condition is corrected, resection of the increased ureteral length will not bring about the clinical improvement that is to be desired. I should like to present a modification that I have observed only once described in the literature, in the management of redundant hydronephrotic sacs.

Many technical refinements are described on the technique of removing redundant hydronephrotic sacs. In resecting these hydronephrotic redundant sacs, it is important that the axis of the incision be in line with the ureteropelvic junction.

In the past few years, I have been handling this problem with a very simple procedure, instead of using some of the more complicated techniques. Three guide sutures are used: one at the ureteropelvic juncture, one at the upper angle of the sac, and one at the medial portion of the sac. With a sling on each side of the upper and lower pole of the kidney, and a long 8-inch straight forceps with striations in the longitudinal axis of the forceps through the margin of the pelvis to be resected, one is able then to resect with precision and exactitude that portion included within the forceps, either with the knife or a straight pointed scissors. With an interlocking suture the remaining portion of the sac is sutured down to the ureteropelvic juncture.

Dr. John A. Benjamin (Rochester, N. Y.): I should like to re-emphasize what Dr. David M. Davis of Philadelphia and others have stressed for years, that probably a good many renal changes are the fault of changes in the ureter itself. Therein lies the pathology to which we should direct our attention.

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HYDRONEPHROSIS IN INFANTS AND CHILDREN

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Hydronephrosis is the commonest abdominal tumor in infants and children and is most often recognized by complete urologic examination performed because of persistent pyuria—so-called chronic pyelitis. In many cases of mild asymptomatic urinary infection perpetuated by unidentified hydronephrosis, an acute exacerbation of the infection results from sudden increase in the urinary obstruction which initially caused the hydronephrosis. Yet an acute infection elsewhere (nasorespiratory, cutaneous, infectious disease) may engender metastatic exacerbation in the injured kidney or by toxic trauma increase the renal debility and lower the local resistance. This induces the clinical picture too commonly designated as acute pyelitis and which, continuing, becomes "persistent acute pyelitis." In some instances the urinary infection is an accidental finding when recurrent gastro-intestinal symptoms for example, are under investigation and routine analysis of a casually collected urine specimen is made. Yet urinalysis may be essentially normal and the urine sterile in the presence of advanced hydronephrosis and grave urinary obstruction. In the present communication the pertinent considerations in 828 cases of hydronephrosis in infants and children are presented; in this series the condition was discovered at autopsy in 316 cases and in 512 was disclosed by urologic investigation.*

ETIOLOGY

Age. The ages of the infants and children reported are shown in table 1 in which it will be noted that in those examined post mortem and those examined clinically, the incidence of hydronephrosis upon the basis of congenital malformations is extremely high, especially in the group less than 1 year of age. Moreover, the condition is frequently either the direct or an important associated cause of early death. Eighty-one per cent of the autopsy group were 12 months of age or less as were 22.2 per cent of the clinical cases with a combined average of 44.7 per cent or nearly half. Not until the fourth decade do the clinical manifestations of hydronephrosis assume comparable importance.

Sex. As shown in table 2, in infants and children hydronephrosis appears to be slightly more frequent in females. In the evaluation of the autopsy findings in this series, however, twice as many males as females were thus examined, while in the clinical group the male:female ratio is 2:3.

Side involved. The occurrence of hydronephrosis is slightly greater on the left side but in nearly half (43.4 per cent) of the cases the lesion is bilateral and

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 26, 1950.

* The statistical summaries recorded here are based on 1) the study by the author of 47,483 autopsies, of which 15,919 were in infants and children (Campbell: Clinical Pediatric Urology, W. B. Saunders Co., Philadelphia, 1951—in press), and 2) 512 *infants and children* with hydronephrosis personally examined and treated.

commonly the result of lower urinary tract obstruction (table 2). While obstruction at or peripheral to the bladder outlet usually accounts for advanced bilateral involvement (table 5), in a surprising number of cases the etiologic factor is bilaterally supravesical and chiefly ureterovesical junction stricture, ureterocele, or ureteropelvic junction blockage by stricture, aberrant vessel, or angulation, and in the order named. Yet combined or multiple obstructions are not uncommon, for example, contracture of the vesical outlet and ureterovesical junction stricture, or ureteral obstruction with secondary vascular blockage. In the tabulation here the primary or proximal blockage is the one recorded.

TABLE 1. *Hydronephrosis in infants and children. Ages in 828 cases*

AGE	SEX	AUTOPSY (15,919)	CLINICAL	TOTAL
		316 cases	512 cases	828 cases
0–6 mo.	M	148 (10,712)	21	169
	F	57 (5,207)	40	97
7–12 mo.	M	39	22	61
	F	12	31	43
13–36 mo.	M	18	46	64
	F	17	78	95
3–6 yr	M	9	56	65
	F	5	85	90
7–10 yr.	M		28	28
	F		65	65
11–15 yr.	M	6	24	30
	F	5	16	21

TABLE 2. *Hydronephrosis in infants and children. Etiology in 828 cases*

	AUTOPSY (15,919)	CLINICAL	TOTAL
	316 cases	512 cases	828 cases
Side Involved			
Right	67	175	242
Left	75	152	227
Bilateral*	174	185	359
Sex			
Male	240	197	437
Female	76	315	391
Location			
Supravesical			
Unilateral	152	322	474
Bilateral	108	102	210
Infravesical†	56	88	144

* Including infravesical obstruction.

† Hydronephrosis Unilateral 16, bilateral 36. With supravesical obstruction: Unilateral 7, bilateral 5.

The numerous conditions both congenital and acquired which may produce hydronephrosis are shown in tables 3 to 6. Here it will be noted that urinary stasis and/or obstruction often results from neuromuscular disease of the urinary

TABLE 3. *Congenital and acquired lesions causing urinary obstruction in children*

- I. Urethra
  - a. Congenital or acquired
    - Phimosis
    - Meatal stenosis
    - Meatal atresia
    - Stricture
    - Cysts
    - Diverticulum
    - Hypertrophied verumontanum
    - Hydrocolpos
  - b. Congenital
    - Posterior urethral valves
    - Penile torsion
    - Abnormal openings
      - Epispadias
      - Hypospadias
  - c. Acquired
    - Polyps
    - Trauma
    - Calculi
    - Tumor
    - Extra-urinary masses, cysts, etc.
- II. Bladder
  - a. Congenital or acquired
    - Contracture of vesical neck
    - Hypertrophy of vesical neck
    - Median bar
    - Median lobe
    - Hypertrophy of inter-ureteric ridge
    - Diverticulum
    - Neuromuscular disease
      - 1. Cord bladder
      - 2. Atonic bladder
  - b. Congenital
    - Anomalies: Exstrophy, reduplicated, bipartate, etc.
    - Trigonal curtain obstruction
    - Ureterocele
    - Hydrocolpos
  - c. Acquired
    - Tumor
    - Prostatic enlargement
    - Prostatic neoplasm (sarcoma chiefly)
    - Calculi
    - Foreign bodies
    - Extravesical masses (sacral teratoma, anterior sacral meningocele, sacro coccygeal chordoma, hydrocolpos, hematocolpos, etc.)
    - Rectal distention by feces, appendiceal abscess, etc.
- III. Ureter
  - a. Congenital or acquired
    - Stricture
    - Stenosis
    - Atony
    - Spasm
    - Cystic dilatation
    - Kinks
    - Angulations
    - Diverticulum
    - Herniation
  - b. Congenital
    - Anomalies of number
    - Anomalies of termination
    - Valves and folds
    - Ureterocele
    - Vascular blockage
      - 1. Primary
      - 2. Secondary
    - Torsion
    - Retrocaval

TABLE 3—(*Continued*)

III. Ureter—(*Continued*)
c. Acquired
Calculus
Inflammation
Ureteritis
Peri-ureteritis
Long-standing infection
Blood clots
Trauma
Ligation
Tumor
Extra-ureteral masses, fibrous bands or enlarged glands which compress the ureter
Fecal distention of rectum

IV. Pelvis and kidney
a. Congenital or acquired
Abnormal ureteral insertion
Stricture at pelvic outlet
b. Congenital
Renal anomalies of number, form, location, size, etc.
Accessory renal vessels
c. Acquired
Calculus
Pelvic outlet blockage by intrarenal or extrarenal neoplasm
Ptosis
Trauma
Infection, especially long-standing
Aneurysm of renal artery (very rare)
Stress hypertrophy of pelvic and calyceal musculature

TABLE 4. *Hydronephrosis in infants and children. Nature and location in 828 cases*

	AUTOPSY (15,919)			CLINICAL			TOTAL
	316 cases			512 cases			828 cases
	Rt.	Lt.	Bil.	Rt.	Lt.	Bil.	
Ureteropelvic Junction and Adjacent Ureter							
Stricture	7	17	10*	33	32	11†	110
Aberrant Vessel	3	8		10	16		37
Stone		1			2		3
Valve (fold)			5				5
Kink‡			1	2	4	2	9
Peri-ureteral Fibrosis	1			2			3
Tuberculosis	3			4	2		9
Postoperative Stricture		1					1
Hydro ½ redupl. Kidney				9	6		15
Localized Hydronephrosis				4	6		10
Other			4				

* U.V.J. Stric. 1 side; U.P.J. on other (2). U.P.J. & U.V.J. on same side (Rt. 5; Lt. 2). Nephroptosis; Bilateral Ureteral Gumma; Uterine Artery Compression; Perinephric Abscess; Inflammatory Parenchymal Edema Causing Compression (Rt. 1).

† Bilateral U.V.J. & U.P.J. (3).

‡ All but one due to distal obstruction.

channels, the central nervous system lesions in the young most frequently being the result of anomalies of vertebroneural fusion (spina bifida, meningocele, etc.).

PATHOLOGY

The renal architectural changes in hydronephrosis are indicated in table 7 (after Hinman); the urographic corollary is given in table 8. The nearer the obstruction is to the kidney, the more rapid and severe are these changes. With increasing intrarenal urinary back pressure, which is the sum of the renal secretory pressure and the hydrostatic gravitational element, the renal parenchyma is progressively compressed between the tense expanding intrapelvic hydraulic mass and the dense renal capsule. There is interference with the parenchymal blood supply and the resulting anoxemia causes grave trophic and other destruc-

TABLE 5. *Hydronephrosis in infants and children. Nature and location in 828 cases*

	AUTOPSY (15,919)			CLINICAL			TOTAL
	316 cases			512 cases			828 cases
	Rt.	Lt.	Bil	Rt	Lt	Bil	
Body of Ureter							
Stricture	9	12	14	29	20	5	89
Stone		1	1		4		6
Valves (fold)	1	1	1				3
Kink			2	2	1	2	7
Peri-ureteral Fibrosis				1			1
Diverticulum					1		1
Other*							4
Ureterovesical Junction							
Stricture	13	14	24	54	52	68	225
Ureterocele	1	6	1	26	17	4	55
Stone	3	1			1		5
Ectopic	2			10	9	2	23
Fibrotic Ureter	1						1
U. opens in Diverticulum	2			1			3
Aberrant Vessel				1			1
Kinks†				9	8	4	21
Tuberculosis				4	2	1	7
Hydro. ½ Redupl. Kidney				21	12	1	34
Prolapsed Ureter					1		1
Other‡							8
Unknown§							29

* Aberrant Vessel (Rt. & Lt. each 1); Tumor Mass (Rt. 1); Tuberculosis (Lt. 1).

† Secondary to Distal Obstruction.

‡ 1. Bladder stone in diverticulum into which ureter opens.
2. Metastasis from sarcoma of uterus.
3. Ectopic kidney.
4. Extra-ureteral compression by retroperitoneal glands, retroperitoneal abscess, vesical diverticulum (each 1).

§ Unrecognized or undetermined neuromuscular vesical disease or long-standing infection was probably etiologic.

tive changes in the cellular structure and these will be most severe in the tissues farthest from the main blood supply. Intratubular distention augments this injury. As the parenchymal damage progresses, glomeruli are altered, many become hyalinized or disappear, while dilatation and shortening of the tubules occur and often with eventual disappearance of many.

TABLE 6. *Hydronephrosis in infants and children. Nature and location in 828 cases*

	AUTOPSY (15,919)	CLINICAL			TOTAL
	316 cases	512 cases			828 cases
	Bil	Rt.	Lt.	Bil	
Bladder Outlet					
Contracture	3	2	2	20	27
Neurogenous	9	4	2	31	46
Valves (fold)	1			2	3
Hypertrophy of trigone	1				1
Sarcoma of bladder	1			1	2
Sarcoma of prostate	1			4	5
Exstrophy of bladder				3	3
Unknown (prob. neurog.)	8			5	13
Urethra					
Posterior					
Valves	6		2	22	30
Hyper. verumontanum	17			5	22
Atresia	1				1
Anterior					
Stricture	1			6	7
Imperforate	1				1
Stenosis of meatus			1	4	5
Phimosis	2				2

TABLE 7. *Progressive changes in hydronephrosis*

TYPE OF URETERAL OBSTRUCTION	TYPE OF PATHOLOGIC CHANGE PROGRESSIVELY PRODUCED	
	Primary	Secondary and Tertiary
1. Complete	Primary atrophy	Secondary atrophy with anuria, or Changes with infection
	Hydronephrotic atrophy	Atrophic pyelonephritis, infected hydronephrosis, pyonephrosis
2 Partial	Hydronephrotic atrophy	Secondary atrophy with anuria, or Changes with infection
3 Progressive (partial to complete)		
4. Temporary (relief after 1 or 2)	Hydronephrotic atrophy	Changes with infection
5 Intermittent (1 or 2, periodically)		Changes with infection or Hydronephrotic repair

The location and nature of the factors concerned in the pathogenesis of hydronephrosis as observed both at autopsy and clinically in the 512 cases in this series are shown in tables 4 to 6. The degree of hydronephrosis observed in the clinical cases and graded from 1 to 4 plus is shown in table 9 (compare with tables 7 and 8). The writer's clinically convenient rule-of-thumb gradation of hydronephrosis is as follows: 1 plus designates pelvicalyceal dilatation half again normal size; 2 plus means twice normal size; 3 plus signifies three times normal size, and 4 plus, four or more times normal size. It is recognized that this classification or grouping is conservative and subject to criticism for it is the functional rather than the anatomic damage we are fundamentally interested in and concerned about. When the pelvis is largely extrarenal and by dilatation more or less buffers the urinary back pressure, calyceal dilatation is usually comparably less than that of the pelvis, while in intrarenal pelvis, great parenchymal damage commonly results from anatomically moderate pelvicalyceal dilatation. In the usual postmortem examination and owing to some ureteropelvicalyceal contraction after death, only the more advanced grades of hydronephrosis are likely to be recognized in the gross specimen. These are chiefly the lesions that urographically one would rate 3 plus or 4 plus, while many of those which urographically would be designated as 2 plus degree will be passed over and practically no 1 plus hydronephroses will be recorded. For the same reason ureterocele is commonly overlooked by the autopsy surgeon. Therefore, in the statistical study of the degree of hydronephrosis present in the cases upon which this communication is based, only those clinically studied are recorded.

TABLE 8. *Urographic changes in hydronephrosis*

LOCATION	EARLY	LATER	ADVANCED*
Pelvis	Increase	Increase	Increase (round sac)
Major calyces	Broadening at base	Broadening throughout	Sacculation
Minor calyces	Flattening or clubbing	Obliterated	Obliterated
Papillae	Shortening	Shortening	Obliterated
Ureter	No change	Change in insertion angle	Elongated (usually not seen in urogram)

The degree and nature of accompanying infection in the clinical cases are shown in table 9 as are associated renal anomalies and pathology. It is noteworthy that a wide variety of nonurologic maldevelopments were found in this series and no system was spared.

Hydronephrosis is of notoriously high incidence in renal reduplication and in these organs as in congenital ureteral obstruction the occurrence of clinical disease is approximately twenty times that found in normally formed kidneys (table 10). In renal reduplication, the superior pelvis is involved nearly twice as often as the lower pelvis, the ureter of the superior pelvis being correspondingly more likely to be strictured, to terminate in ureterocele or to be ectopic (table 10). In several of our cases of bilateral hydronephrosis, the obstructing lesion was at the ureteropelvic junction on one side and at the ureterovesical junction on the other, or at other and different levels on each side.

Other complicating pathologic conditions such as stone, ureteral kink and so

TABLE 9. *Hydronephrosis in infants and children. Pathology in 235 clinical cases*

	PELVIS											
	Single				Reduplicated							
					Right			Left			Both	
	Rt.	Lt.	Bil.	Total	Up.	Low.	Both	Up.	Low.	Both	Up.	Low.
Degree												
1 plus	27	16	9	52	1	3			3			1
2 plus	13	16	11	40		2		1	4			1
3 plus	8	13	7	28	3	2	1	3	1			1
4 plus	18	29	29	76	6		3	4	3	2		
Not record.	8	2	5	15	1					1		1
Infection												
Present	44	43	62	149	10	6		7	7	2		4
None	5	6	3	14	1				1	1	2	
Not record.	13	10	15	38	1			1				
Pyonephrosis												
Nontuberc.	1	4	2	7	5	1	1	4		1		
Hydro. Atrophy	3	8	5	16					1	1		
Kidney												
Solitary	2	1		3								
Hypoplastic	1			1								
Reduplicated	17	17	15	49								
Horseshoe			2	2								
Ectopic	1	1	1	3								
Malrotated	2			2								
Tumor		1		1*								

* Early Wilms'; resected left lower segment of redupl. left kidney.

TABLE 10. *Hydronephrosis in infants and children. Pathology: Pelvic reduplication in 235 clinical cases*

			Rt.	Lt.	Bil.
Kidney-Reduplicated		Ureter-Reduplicated			
Right	24	Involved Pelvis			
Left	21	Stricture			
Bilateral	20	U.P.J.	1	1	
Involved Pelvis		Body	1	2	
Upper	29	U.V.J.	14	7	3
Lower	21	Ureterocele	11	6	1
Both	14	Ectopic			
Ureter-Reduplicated		Dil. Orifice	3	6	
Complete		Str. Orifice	3		
Unilateral	33	Kink	3	1	
Bilateral	10	Vascular Obstr.	2		
Incomplete		Tortuous	2	2	
Unilateral	9				
Bilateral	1				

forth are shown in tables 4, 5 and 6. The urinary stasis favors calculous formation and chiefly in the renal pelvis.

SYMPTOMS

Hydronephrosis produces no characteristic syndrome of its own (table 11). A palpable hydronephrotic mass in the upper lateral abdomen may be the only manifestation and in some cases has even been discovered by the child. In hydronephrosis the clinical syndrome inadequately designated as chronic pyelitis commonly exists as it did in two-thirds (64.7 per cent) of the 235 recent cases of this series urologically studied. Persistent or recurrent pyuria, chills, fever, pain in the affected side and often with periodic hematuria are the most frequent manifestations. With exacerbation of smoldering infection in the hydronephrotic kidney, the diagnosis of persistent acute pyelitis is commonly made and the condition demands immediate urologic examination.

With secondary vesical involvement by infection or when there is obstruction at or peripheral to the bladder outlet, disturbances of urination with frequency, urgency, nocturia, dysuria, dribbling, incontinence and even "enuresis" often exist. In some instances the incontinence results from ectopic ureteral opening above which there is hydronephrosis. Gastro-intestinal disturbances are outstanding symptoms in half of all cases of hydronephrosis in the young and may result from compression of the bowel by the renal mass, or reflect toxemia consequent to urinary infection and/or renal functional damage. Loss of appetite, anorexia, nausea, vomiting, failure to grow, loss of weight and strength are the usual symptoms. As the hydronephrosis becomes large, the bowel is compressed; in a three-year-old boy with massive left hydronephrosis, the descending colon was pushed across the abdomen to course parallel and adjacent to the ascending colon. Constipation was a dominant symptom. Neurologic manifestations such as drowsiness, lethargy, hyperirritability, nervousness are frequent in these cases and reflect the irritation of the central nervous system by the urinary toxemia. The symptoms in the clinical cases are shown in table 11.

TABLE 11. *Hydronephrosis in infants and children. Symptoms in 235 clinical cases*

Pyuria	149	Chronic Uremia	6
Fever	93	Nervous Manifestations	
Pain	60	Convulsions	9
Hematuria	30	Headaches	3
Mass	15	Marasmic	4
Gastro-intestinal		Stuporous	2
Nausea	9	Toxic	9
Vomiting	43	Sepsis	1
Anorexia	5	Retention	
Loss of Weight	1	Acute	5
Failure to Gain	3	Chronic	23
Diarrhea	8	Frequency	38
Constipation	12	Dribbling	22
Edema—each	1	Dysuria	21
Eyes, head, scrotum		Enuresis	16
		Prolapsed Ureterocele	3

DIAGNOSIS

The history of chronic pyuria should at once suggest the presence of hydronephrosis. As a corollary, pyuria exists in 60 to 95 per cent of hydronephroses and albuminuria in half to three-fourths. The diagnosis will be confirmed only by adequate, and usually complete, urologic examination, the indications for which are given in table 12, and when these manifestations are present, hydronephrosis is commonly found. A tenth to a fourth of hydronephroses in children are palpable (table 13). Yet the diagnosis of hydronephrosis by palpation alone is extremely hazardous in view of the high incidence of renal, adrenal and cystic tumors which upon physical examination alone may suggest tense hydronephrosis. Renal tuberculosis, calculous pyonephrosis, perinephritis, acute or chronic pyelonephritis are also to be considered in the differential diagnosis.

In the diagnostic survey excretory urography commonly suggests that hydronephrosis exists and may identify complicating calculous disease or diverticula, for example. Although today we almost always make a preliminary or "scout" excretory urographic study, definitive pyelographic delineation requires retrograde pyelography and preferably bilateral to demonstrate the morphologic and functional integrity of the opposite kidney as well. Moreover, in hydronephrosis and as shown in tables 9 and 10, the hydronephrotic organ is often anomalous, being reduplicated, horseshoe, ectopic or cystic, or even tumor bearing.

TABLE 12. *Indications for urologic examination in infants and children*

1. Pyuria
    a. acute persistent
    b. chronic
2. Disturbances of urination—dysuria, frequency, urgency and so forth
3. Hematuria (except acute nephritis)
4. Abdominal pain
5. Abdominal tumor
6. Anomaly of the external genitalia
7. Urogenital injury
8. Spinal cord injury and disease
9. Enuresis
10. Renal insufficiency
11. Retarded growth
12. Hypertensive vascular disease

By complete examination, reduplicated kidneys or other conditions of surgical import are commonly disclosed even though not always suggested by the excretory study. Moreover, at operation a clear cut ureteropyelogram is of great comfort and guidance for the surgeon, particularly when renal resection is required. Because of the unreliability and inadequacy of excretory urographic studies for the demonstration of upper urinary tract surgical disease in over half of all cases in infants and children, and because of some unfortunate experiences resulting from reliance on this urographic demonstration alone, retrograde pyelography is routinely performed preoperative by the writer.

The laboratory evidence merits serious consideration not only in formulating the therapeutic program but the prognosis as well (table 13). In the treatment of hydronephrosis this is of prime consideration when the problem of preliminary drainage (nephrostomy, cystostomy and so forth) arises because of the gravity of the patient's condition or conservation of the kidney is demanded. The laboratory studies should include not only careful urinalysis of aseptically collected specimens (by catheterization in females of all ages) but the bacteriology of the urine. Tests of renal function are made, notably phenolsulfonphthalein intravenous excretion, as well as the blood chemistry estimations as they may disclose nitrogenous retention, the carbon dioxide combining power and, in cases of long-standing renal damage, the blood chloride, serum phosphorus and calcium, with a view to recognition of possible primary or secondary renal hyperparathyroidism.

TABLE 13. *Hydronephrosis in infants and children. Diagnosis in 285 clinical cases*

Palpation-Palpable Mass	20	Urinalysis	
Cystography	33	Normal	14
Pyelography		Albumin	118
Excretory	108	Pyuria	156
Retrograde	223	Blood	71
Urethrography	5	Bacteria (culture)	
Prev. Urologic Exam. and/or Treatment	101	Gram-positive cocci	
		Streptococci	53
Rectal Paralysis	14	Staphylococci	106
		Gram-negative bacilli	
		"B. coli"	106
		Ps. aerugenosa	10
		Tuberculosis	1
		Mixed	85
		Sterile	18

PROGNOSIS

This depends upon 1) the degree of renal damage including that due to the ravages of infection, and 2) the adequacy of treatment. Unfortunately there is bilateral involvement in at least a third of the clinically recognized cases. In a third to a half of all cases of unilateral hydronephrosis, adequate treatment will demand nephrectomy because the condition has progressed unidentified and the renal injury is irreversible and/or irreparable. Here the renal damage and the required nephrectomy may be looked upon as the fruits of medical neglect. In children with unilateral hydronephrosis and a sound kidney on the other side, the surgical mortality is negligible and few will be dead within 10 years. In children with well-developed bilateral hydronephrosis and without treatment two-thirds will be dead within ten years. In most cases death will result from renal failure with complicating urinary sepsis but terminal pneumonia in these debilitated patients is of high incidence. Yet in several of our patients first seen in infancy with advanced bilateral hydronephrosis and whose outlook at the time seemed hopeless, multiple stage conservative surgical therapy has amazingly restored them to apparent good health, albeit with the scars of irreversible

TABLE 14. *Hydronephrosis in infants and children. Treatment in 512 cases*

None or refused	49	Surgery	
Chemotherapy		Kidney	
Only	8	Nephrectomy	40
And as follows:	251	Nephro-ureterectomy	31
Dilation		Ureteroheminephrectomy	25
Ureter	140	Horseshoe	
Bladder neck	17	Resection	3
Urethra		Symphysiotomy	3
Body	3	Nephrostomy	
Meatus (many)		Temporary	
Indwelling catheter	84	Unilateral	16
Temporary	77	Bilateral	16
Ureter	18	Permanent	
Corset for nephroptosis	1	Unilateral	14
		Bilateral	4
		Pyelostomy	1
		Pyelotomy	1
		Pelvic Resection	6
		Nephropexy*	5

* In connection with other renal surgery.

TABLE 14A. *Hydronephrosis in infants and children. Treatment in 512 cases*

URETER	UNILAT.	BILAT.
Ureterostomy	4	3
Cutaneous (permanent)	1	2
Lithotomy	3	
Ureterolysis	2	
Ureteroplasty		
U.P.J.		
Resection	5	
Y-plasty	11	1
Body		
Incision	3	
Resection	5	2
U.V.J.		
Incision		
(Meatotomy)		
Cystoscopic	11	5
Transvesical	7	6
Ureteromeatoplasty	5	6
Ureteroneocystostomy	5	1
Aberrant Vessel Resection	12	
Ureterocelectomy		
Suprapubic	11	
Transurethral	10	
Excision prolapsed	1	
Ureterosigmoidostomy		2

damage in their kidneys. Some of these are now in college. Here, as in the treatment of neoplastic disease, only by treating the many, do we cure the few. In a third of the cases in the autopsy series, death was directly attributable to the hydronephrosis and its complicating infection, renal failure and urinary toxemia.

TABLE 14B. *Hydronephrosis in infants and children. Treatment in 512 cases*

Bladder		Urethra	
Cystostomy		Valve Resection	11
Temporary	38	Urethrotomy	
Permanent	18	Internal	2
Diverticulectomy	3	External	1
With ureterocelectomy	2	Meatotomy	
Cystolithotomy	2	(many)	
Litholapaxy	1	Only	5
Bladder neck resection			
Suprapubic		Cystoprostatectomy	2
V-wedge	9	(sarcoma prostate)	
Trigonal curtain	1		
Transurethral		Incision Imperforate	
Punch	6	Hymen (hydrocolpos)	2
Resectoscopic	22		

TABLE 15. *Hydronephrosis in infants and children. Results in 512 clinical cases*

	NONOPERATIVE	SURGICAL	TOTAL
Cured*	14	70	84
Improved			
With urine sterile	19	22	41
Without urine sterile	17	33	50
Urine culture unknown			78
Unimproved			
Stasis persists	10	27	37
Died			
Before Treatment	6		6
Postoperative		13	13
Urinary sepsis	4	9	13
Uremia	5	7	12
Urologic disease			25
Other causes			19
Lost or result unknown			129
No treatment or refused			49

* Both infection and stasis.

TREATMENT

This will be based upon the pathologic anatomy as urographically delineated and in correlation with which the renal function, particularly of the remaining kidney, as well as the general condition of the patient must be evaluated. In several infants intensely ill with advanced bilateral infected hydronephrosis, initial bilateral nephrostomy for periods up to six months has been used. In the rare instance this must be permanent.

Unfortunately nephrectomy in some form is demanded in at least a third of these cases coming to operation. In some children conservative plastic operation will succeed in saving the kidney; the prospects of this favorable outcome are vastly increased by simultaneous intensive chemotherapy and/or antibiotic therapy.

The technical procedures employed in the treatment of hydronephrosis and according to surgical and clinical indications are shown in table 14 in which their application in the clinical series here reported is enumerated.

Results of treatment. The results of therapy in these cases are shown in table 15. Attention is directed to the desirability of precision in classifying the therapeutic results. A child symptomatically relieved by nephrectomy yet in whom urinary infection or a stasis-producing condition persists, is not cured. In hydronephrosis a patient is cured only when urinary stasis has been eradicated, the urine is sterilized, and renal function adequate to support life for a reasonable number of years has been achieved. Yet many patients with long-standing renal lesions in which irreversible damage has occurred or a condition such as irremediable neuromuscular vesical disease exists, can never be cured in the strict sense.

SUMMARY

Hydronephrosis is the commonest abdominal tumor of childhood at which age it most often results from congenital causes. Rarely the obstruction is acquired as in urinary calculous disease or spinal injury. The pathologic changes are fundamentally those of renal destruction and are anatomically characterized by pelvicalyceal dilatation, parenchymal thinning, sclerosis and destruction of secretory elements. The commonest clinical manifestation is persistent pyuria, too often designated as chronic pyelitis, both inadequately investigated and treated. Less frequently the appearance of a mass or pain in the loin or abdomen directs attention to the lesion. Acute exacerbation of smoldering infection associated with infected hydronephrosis generally causes the diagnosis of persistent acute pyelitis to be made. The indications for complete urologic examination of children with hydronephrosis are many but pyuria, persistent or acute, pain or a mass in the loin or abdomen, hematuria and reflex vesical disturbances are the usual symptoms. The diagnosis is readily suggested by excretory urographic study and can be made absolute by satisfactory retrograde pyelography and preferably bilateral. Treatment is according to the specific surgical indication and occasionally conservative therapy by instrumental dilation is successful. In most cases operation is necessary although it may often be conservative surgery. Yet in a third to a half of the children in whom hydronephrosis is clinically recognized, the severity of the renal damage warrants only total nephrectomy. With early identification and proper treatment, the majority of these kidneys should be saved as well as many lives.

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THE EFFECTS OF INTRARENAL HYDRONEPHROSIS ON THE COMPONENTS OF THE RENAL CORTEX

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This paper deals with the histopathology and hydrodynamics of the various components of the kidney in the development of intrarenal hydronephrosis, excluding the factor of infection. Grossly, the whole kidney becomes enlarged and its surface lobulated due to the dilatation of the individual calyces. As the hydronephrosis reaches the final state of complete atrophy of the kidney the whole organ appears as a thin-walled sac. Rupture of these thin-walled sacs is relatively rare but does occur.

Our interest particularly is focused upon the pathology and physiology of the calyces, the vascular system and the various tubules that comprise the cortex and medulla of the kidney. Studies of the interior of the pelvis by Hinman, Strong, Oliver and Ponfick in experimental hydronephrosis would indicate that as the pelvis becomes distended a certain order of pathological events takes place. The papillae are torn apart causing an irregular oval depression from whose margin radiate interrupted collecting tubules. In time these interrupted tubules become closed with connective tissue and their openings covered with epithelium. As the pelvis increases in size the cortex becomes thinner due to the atrophy of the various tubular structures. Ponfick states that the rate of accumulation of the pelvic fluid and the rate of atrophy of the parenchyma are in agreement.

VASCULAR CHANGES

As the pelvis becomes distended one or all of the calyces become broader, affecting both the radial and circumferential vessels. The former will be foreshortened and crinkled, while the latter will be lengthened, and the total blood flow will thus be reduced through both arterial systems. Those portions of the kidney supplied by the most distal vessels will atrophy first. Hinman has well demonstrated this pathological change and concludes that the loss of nutrition plays a large part in the development of renal peripheral atrophy and the subsequent development of hydronephrosis. Trueta substantiates these vascular changes in his description of the greater and lesser circulation of the kidney, the greater circulation being through the medulla and the lesser through the cortical portion of the kidney.

THE GLOMERULI

The juxtamedullary glomeruli and associated medullary vascular channels offer a pathway of lesser resistance for circulation than through the superficial glomeruli in the cortex. Furthermore, the interlobular veins and cortical intertubular capillaries are filled by reflux from the vessels draining the medulla.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 26. 1950.

The cortical glomerulus has an efferent vessel which is small in caliber and which breaks up to form the cortical interlobular capillary network; while the juxtamedullary glomerulus has an efferent vessel which is large and passes into the medulla to divide into the vasa recta. The juxtamedullary glomeruli and vasa recta form a by-pass through the medulla. This "by-passing" of the blood causes anemia, ischemia and atrophy, and as the hydronephrosis increases in size the cortical portion of the kidney is the first to atrophy.

The first changes within the glomerulus are the widening of Bowman's space and shrinking of the capillary tuft due to loss of blood supply. A cleft often appears within the tuft. Later in the pathological process Bowman's membrane becomes puckered, connective tissue proliferation appears and finally a hyalinization within the tuft. The glomeruli may in neighboring areas show cystic changes and vary in size and shape due to the pressure in the pelvis and contracture of the connective tissue in the cortex.

TUBULAR CHANGES

The tubular changes are closely related to those of the pelvis and the vascular tissues, and nephrons or groups of nephrons are affected. The tubules degenerate in groups mainly from anemia, because several tubules have a common blood supply. What effect the free capillary anastomosis of the tubular bed has is not known. Group distribution of hydronephrotic change is a definite characteristic and is related to vascular change. The immediate effect of back pressure is venous congestion not unlike an inflammatory reaction with tubular dilatation. Irregular changes in the intrapelvic pressure such as are seen in intermittent hydronephrosis will cause irregular circulation and irregular changes in the tubules, a collapse and atrophy in some while in the freer areas of circulation an increased functional activity and even a compensatory hypertrophy of the tubules may occur. As the hydronephrosis progresses these tubules are deprived of their blood supply and degenerate in groups. Usually the convoluted portions degenerate first, then the looped portions and the medullary glomeruli are the last to resist. Group resistance and group atrophy are characteristics of hydronephrosis, hence the saccular areas which are seen grossly on exposure of an hydronephrotic kidney.

A detailed study of the various tubules by Oliver and Strong throws much light on the progressive pathology of the tubular elements of the nephron. The first changes occur in the proximal convoluted tubules. Their lumina show increase in caliber, and their epithelial cells become flattened. Some of these tubules may be compressed with resulting degeneration of their epithelial cells and vacuolization of their cytoplasm, followed by progressive atrophy and proliferative connective tissue formation. The proximal convoluted tubules form the chief bulk of the organ, hence their rapid atrophy is a factor of greatest importance in facilitating the accumulation of pelvic fluid and determining the architecture of the hydronephrotic kidney. The loops of Henle at first are sharply distinguished from the proximal convoluted tubules, for they remain small and thin-walled and never increase in size or become dilated. In the latter stages they may be represented by strands of tissue and be confused with connective tissue. The collecting tubules at first increase in size irregularly in the medulla and cortex, later become fragmented, and end blindly at the pelvis with a saccular deformity. Cortical tubules become interrupted and persist as blind structures varying in size and form and not infrequently as a linear series of minute spherical cysts surrounded by connective tissue. The cortical portion of the kidney first shows evidence of change in the collecting tubules, later the medullary portion, and finally the tubules adjacent to the pelvis are affected. For a time the fluid flows through these short, dilated, central collecting tubules to be absorbed by the distal convoluted tubules. Blood in the urine in hydronephrosis may come from the distal convoluted tubules. Backflow is impossible in the interrupted convoluted tubules in the lateral area, while it occurs in some of the nephrons in the intermediate area, and there may be a flow directly towards the pelvis. The interstitial tissue stroma at first is edematous, but later infiltration of polymorphonuclear leukocytes and round cells occurs. Scars appear about the larger vessels. Early structural changes in the blood vessels appear insignificant, although early congestion of the capillaries and veins occurs. Compression of the glomerular capillaries is followed by hyalinization of the smaller arterial branches and connective tissue proliferation within the capillary tuft. The development of fibrosis of the interstitial tissue causes retraction and tortuosity of the tubules, but the resistance to molding and loss of continuity is evidenced by an amazing restitution of physiological activity when the blood flow is returned after removal of the obstructing factor. This reversible phenomenon of physiology is exemplified in the successfully operated hydronephrotic kidneys.

RATE OF HYDRONEPHROTIC DEVELOPMENT

The size of the pelvis does not necessarily represent the amount of atrophy present in the kidney. Many large extrarenal hydronephroses occur in kidneys with exceptionally well-preserved functions, while a moderate-sized hydronephrotic kidney may show much atrophy of the cortex. Clinically we encounter relatively large hydronephrotic sacs in children and in middle-aged patients who have but few symptoms. Other patients have symptoms compatible with a diagnosis of hydronephrosis for many years without a greatly distended pelvis. Occasionally in cases with ureteral calculi we obtain excretory urograms which show the gradual development of a certain amount of dilatation of the ureter and pelvis with blunting of the calyces and thinning of the cortex of the kidney. Rarely do we have an opportunity to observe clinically and to correlate the rate of hydronephrotic development with the factors which are responsible for the progressive pathological lesion.

The first factor which is essential for hydronephrotic atrophy is back pressure. Experimenting with dogs, Cushny and Barney have demonstrated that if the ureter be ligated and the intrapelvic pressure be recorded the secretory force of the kidney will raise the mercury in the manometer from 50 to 70 mm., but after several hours it will gradually drop. The administration of diuretics produces little influence on the intrapelvic pressure and then only temporary. Any change in blood pressure or degree of obstruction, activity or position of the patient would influence the intrapelvic pressure. Hinman could not demonstrate any influence of hydration and dehydration on the rate of hydronephrotic development. Even though a splanchnicotomy causes an intrarenal vasodilatation and an increase in the renal blood flow with a prolonged diuresis there is no modification in the rate of hydronephrotic atrophy. Neither diuresis nor oliguría is effective in the developing hydronephrotic kidney.

Hinman, experimenting with a series of rabbits, ligated the ureter, partially ligated the renal vein, the renal artery and lastly performed decapsulation. In the absence of collateral circulation he found that all of these factors hastened hydronephrotic atrophy because of the lack of nutrition to the glomeruli and tubules. Hence we may expect that any distention of the renal pelvis which causes pressure on the renal vein and artery would satisfy conditions favorable for a relatively rapidly-developing hydronephrotic atrophy, provided that the pressure was constant and progressive. Secretion of some urine must continue with back pressure; but if the secretion ceases blood flow stops and primary atrophy follows. Clinically, infection occasionally supervenes, produces an anuria and blots out the hydrodynamic hydronephrotic factor, so that the patient either succumbs to the infection or the kidney is transformed into an insignificant mass of fibrous tissue. The rate of hydronephrotic development depends on the degree of urinary obstruction, renal blood flow, fluid absorption from the pelvis and atrophy of the nephrons.

ABSORPTION AND BACK FLOW

Back pressure, curtailment of the blood flow and diuresis do not embrace all the mechanical hydrodynamic factors at play in the production of hydronephrosis. There must be a continuous secretion of urine. Since it can not all escape through the ureter it must either be absorbed or escape through some mechanism of backflow into the circulation. The excreto-secretory units will continue to function as long as the intrapelvic pressure remains lower than the secretory pressure, for when they become equal secretion of urine ceases. The relationship of these two forces must always exist in this order, otherwise the pelvis of the kidney would not enlarge with fluid. As the hydronephrosis progresses the secretory function of the kidney diminishes. Complete atrophy does not come into being until long after the function is lost. As long as a hydronephrosis exists there must be some exchange of fluid within the pelvis. The fluid of an early hydronephrosis contains practically all the contents of a normal urine with urea, salt, etc.; but in the late stages of development there is less urea, some sugar, and finally only salt and water. It can not well be compared to a fresh-water pond with an inlet and outlet of running water, because the fluid in the pelvis changes its character in the progression of thė hydronephrosis This change in the fluid content of the pelvis is brought about by tubular reabsorption until the tubules are destroyed. Loeb has shown that alkaline solutions promote permeability of the semi-permeable membrane of the pelvis, while acid urine prevented this permeable action. Hence patients with an acid urine would have an accelerated rate of hydronephrotic development.

Hinman's experimental pyelovenous backflow and direct connection with lymthey may be represented by strands of tissue and be confused with connective tissue. The collecting tubules at first increase in size irregularly in the medulla and cortex, later become fragmented, and end blindly at the pelvis with a saccular deformity. Cortical tubules become interrupted and persist as blind structures varying in size and form and not infrequently as a linear series of minute spherical cysts surrounded by connective tissue. The cortical portion of the kidney first shows evidence of change in the collecting tubules, later the medullary portion, and finally the tubules adjacent to the pelvis are affected. For a time the fluid flows through these short, dilated, central collecting tubules to be absorbed by the distal convoluted tubules. Blood in the urine in hydronephrosis may come from the distal convoluted tubules. Backflow is impossible in the interrupted convoluted tubules in the lateral area, while it occurs in some of the nephrons in the intermediate area, and there may be a flow directly towards the pelvis. The interstitial tissue stroma at first is edematous, but later infiltration of polymorphonuclear leukocytes and round cells occurs. Scars appear about the larger vessels. Early structural changes in the blood vessels appear insignificant, although early congestion of the capillaries and veins occurs. Compression of the glomerular capillaries is followed by hyalinization of the smaller arterial branches and connective tissue proliferation within the capillary tuft. The development of fibrosis of the interstitial tissue causes retraction and tortuosity of the tubules, but the resistance to molding and loss of continuity is evidenced by an amazing restitution of physiological activity when the blood flow is returned after removal of the obstructing factor. This reversible phenomenon of physiology is exemplified in the successfully operated hydronephrotic kidneys.

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The hydrodynamics of hydronephrosis depends on ureteral or ureteropelvic obstruction and renal secretion, for neither diuresis, hydration or dehydration, or splanchnicotomy affect the rate of development. There must always be some urinary secretion, although as the hydronephrosis develops the kidney function diminishes. Evidence is shown that the fluid of the pelvis escapes through several avenues: 1) if alkaline, through the semipermeable membrane of the pelvis: 2) by tubular backflow through the calyx: 3) by pyelovenous backflow: 4) by pyelolymphatic backflow; and 5) by "sinus extravasate" into the tissue about the hilum of the kidney: and that these factors, together with obstruction and urinary secretion, are in constant effect until the hydronephrotic atrophic state is complete.

CONCLUSION

Two facts are self evident:

a) From the study of the pyelograms, pathology and histodynamics of the renal components, one can ascertain how much permanent damage has taken place in the nephrons in hydronephrosis.

b) One can avoid the embarrassment of a secondary nephrectomy by doing a primary nephrectomy instead of a plastic repair which will later necessitate a nephrectomy.

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REFERENCES

Barney, J. D.: The influence of the venous collateral circulation of the kidney on hydronephrosis. Ann. Surg., 65: 557–601, 1917.

Cushny, A. R.: The Secretion of Urine. New York: Longmans, Green & Co., 1917; second edition, London: Longmans, Green & Co., Ltd., 1926.

Hinman, F.: The Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1935.

Loeb, J.: Salts and animal membranes. J. Biol. Chem., 31: 343, 1917.

Oliver, J.: New directions in renal morphology. A method, its results and its future. Harvey Lect., 40: 102–155, 1944–1945.

Olsson, O.: Studies on back-flow in excretion urography. Acta Radiologica, supplement 70, Lund, 1948.

Ponfick, E.: Beitr. z. path. Anat. u. z. allg. Path., 49: 127, 1910.

Strong, K. C.: Plastic studies in abnormal renal architecture. V. The parenchymal alterations in experimental hydronephrosis. Arch. Path., 29: 77, 1940.

Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M. and Prichard, M. M. L.: Studies of the Renal Circulation. Springfield, Ill.: Charles C Thomas, 1947.

Wood, A. H.: Unilateral renal chyluria. J. Urol., 21: 109, 1929.

phatic channels offers another avenue for the escape of fluid from the renal pelvis. The extensive observations of Olsson support the contentions of Hinman. Wood first demonstrated the lymphatic connection of the pelvis in a case of chyluria on whom he had performed a retrograde pyelogram. Since then, numerous clinicians, including the author, have made such observations. The pyelogram in these patients depicts a linear shadow extending from the pelvis of the kidney toward the median aspect of the patient. In contrast, tubular backflow presents a bursting tuft effect at the calyx in the pyelograms. Richards observed a mercury droplet in the frog's kidney to flow from the tubules into the vein so that tubulovenous backflow is possible in the frog, although he did not demonstrate the exact point of communication. In the normal papilla there is a proliferative type of epithelium around the mouths of the ducts so that as the hydronephrosis develops it produces a radial distention of the papillary area and causes the mouths of the ducts to open, allowing a free communication between the pelvis and the tubules. If the ureteral obstruction be relieved the kidney will secrete the fluid with the same contents as is found within the hydronephrotic pelvis which means a total absorption of the pelvic contents.

Olsson believes that both pyelovenous backflow and pyelolymphatic backflow occur, but that they are not common. He prefers to explain the hydromechanics of the backflow as a sinal extravasate. This hydromechanical condition is brought about by the rupture of the epithelial lining of a tubule with extravasation along the interlobular vessels. Oliver has demonstrated that the distal convoluted tubules in hydronephrosis are subject to much diverticular formation. May not some of these diverticula of the convoluted tubules rupture under back pressure, thus causing the sinus extravasation of Olsson?

It is quite evident, then, that the hydromechanics of the developing hydronephrosis involve the factors of obstruction, of renal secretion, tubular absorption, pyelovenous backflow, pyelolymphatic backflow and interstitial backflow and that these factors are in constant effect until renal secretion ceases and the hydronephrotic atrophic state is complete.

SUMMARY

The first factor in the development of hydronephrosis is back pressure. With the distention of the pelvis and calyces the blood flow through the radial and circumferential arteries is reduced so that the earliest vascular change occurs in the lesser circulation, exemplified by the atrophy of the cortical glomeruli. The last glomeruli to be affected are those in the medulla. Tubular changes are closely related to the vascular changes. Groups of nephrons are involved in the pathological changes. The first tubular change occurs in the convoluted tubules whose lumina become increased in caliber and whose epithelium becomes flattened and later atrophies. The loops of Henle remain at first small and thin-walled, never dilated, but finally atrophy to become only strands of connective tissue. The collecting tubules increase in size irregularly in the cortex and medulla, become fragmented and interrupted and end blindly as a saccular deformity. Fibrosis of the interstitial connective tissue modifies the configuration of the tubules.

The hydrodynamics of hydronephrosis depends on ureteral or ureteropelvic obstruction and renal secretion, for neither diuresis, hydration or dehydration, or splanchnicotomy affect the rate of development. There must always be some urinary secretion, although as the hydronephrosis develops the kidney function diminishes. Evidence is shown that the fluid of the pelvis escapes through several avenues: 1) if alkaline, through the semipermeable membrane of the pelvis; 2) by tubular backflow through the calyx; 3) by pyelovenous backflow; 4) by pyelolymphatic backflow; and 5) by "sinus extravasate" into the tissue about the hilum of the kidney; and that these factors, together with obstruction and urinary secretion, are in constant effect until the hydronephrotic atrophic state is complete.

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Cushny, A. R.: The Secretion of Urine. New York: Longmans, Green & Co., 1917; second edition, London: Longmans, Green & Co., Ltd., 1926.

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Loeb, J.: Salts and animal membranes. J. Biol. Chem., 31: 343, 1917.

Oliver, J.: New directions in renal morphology. A method, its results and its future. Harvey Lect., 40: 102–155, 1944–1945.

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Ponfick, E.: Beitr. z. path. Anat. u. z. allg. Path., 49: 127, 1910.

Strong, K. C.: Plastic studies in abnormal renal architecture, V. The parenchymal alterations in experimental hydronephrosis. Arch. Path., 29: 77, 1940.

Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M. and Prichard, M. M. L.: Studies of the Renal Circulation. Springfield, Ill.: Charles C Thomas, 1947.

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CARBUNCLE OF KIDNEY

S. J. PEARLMAN

A localized suppurative lesion of the kidney presenting all the pathological characteristics manifested by a carbuncle of the skin might justifiably be termed a renal carbuncle. The condition was first described by Israel in 1891 and since then over 200 cases have been reported in the literature. Because of the fact that these lesions are secondary as a rule to some furuncle elsewhere in the body, or to an acute infection, the organism most often recovered is the staphylococcus, and the lesion has been described as a staphylococcal abscess of the kidney. This is not always true since other organisms may be responsible for the lesion. In the two cases to be reported, Pseudomonas aeruginosa and Bacillus coli were recovered on culture. Cortical infections, the result of blood stream invasions, are most often staphylococcal in origin. But when the cortical abscesses are the end result of ascending suppurative pyelonephritis and lymphatic extension, the organisms are usually the bacillus coli.

Some difference of opinion exists as to what are the primary changes after the infecting organisms reach the kidney through the blood stream. Some writers believe that an infected embolus becomes caught at the point of branching of a small artery and that after riding in this point of obstruction for sometime, it is gradually broken up by the force of the blood stream and that these fragments, containing myriads of bacteria, are carried to neighboring parts of a small section of the kidney, setting up small adjoining abscesses which coalesce to form a carbuncle. Other observers contend that instead of an embolus or fragments of emboli being carried to adjoining areas as the result of obstruction, a few organisms are trapped at one point, multiply, and by spreading along the lymphatics, produce many points of suppuration.

The description of carbuncle of the kidney varies with the time of operation, whether it is performed early or late. The lesion starts in the cortex but there is early extension to the fibrous capsule and often a penetration of this capsule with involvement of the perinephric fat and the formation of a perinephric abscess. Quite often, one finds a fistula leading from the carbuncle into an infected perinephritic cavity. Microscopic sections of a carbuncle show lymphocytes, plasma cells and polymorphonuclear leukocytes. The offending organism can usually be seen scattered through the section. It is often possible to differentiate the individual minute abscess by the strands of connective tissue separating them.

The preoperative diagnosis of renal carbuncle is usually difficult to make and most cases are operated on for cortical infection, at which time the true nature of the lesion is revealed. Excretory urograms are not helpful since a carbuncle of the kidney does not involve the renal pelvis. With associated perinephritis or perinephric abscess, obliteration of the psoas muscle shadow may be present on the infected side with scoliosis of the spine. Certain points, however, in the history, physical findings and laboratory studies may suggest the diagnosis. The history of a recent skin infection is frequently obtained. Recurring chills and fever indicate a bacteremia and when accompanied by tenderness over the kidney point to cortical infection. Although the urine is often negative on microscopic examination, a specimen which is centrifuged at high speed for one or two hours may reveal micro-organisms. Leukocytosis, with or without secondary anemia is present. Occasionally, a "bump" on the outer surface of the kidney seen on the urograms is suggestive of the presence of a carbuncle.

Difference of opinion exists as to the proper surgical treatment. While nephrectomy was practiced quite routinely in the earlier cases, conservative surgical management has proved quite successful in the cases reported later. These have varied from: 1) decapsulation and drainage down to the carbuncle; 2) incision and drainage; 3) currettment and drainage; 4) cauterization; 5) enucleation; 6) excision; 7) partial nephrectomy.

Nesbit and Dick in 9 cases reported nephrectomy in only 1 case. They used drainage of the carbuncle in the remainder of the cases with complete healing in every instance. Simple drainage of a perinephric abscess will often prove inadequate when a carbuncle is the underlying lesion and it is for that reason that a careful inspection of the kidney should be made when such an abscess is encountered. When a carbuncle is found, the procedure to be followed will be determined by several factors, namely, a) the extent of the parenchymal destruction; b) the general condition of the patient; c) and the condition of the opposite kidney. If the major portion of the kidney is hopelessly destroyed by a large single carbuncle, or if the patient is so debilitated as to require immediate relief of the septic burden, then a rapid primary nephrectomy should be carried out. Otherwise, any one of the conservative surgical measures mentioned above may be employed.

Mooney mentions the comparative ease with which the carbuncle may be shelled out from its capsule of inflammatory tissue. It is obvious this procedure is possible only when the lesion has escaped detection for some time. Each of the 2 cases to be reported was complicated by the presence of urinary calculi, one of which proved to be albuminous.

CASE REPORTS

Case 1. F. C., a man 47 years of age, was first seen on August 21, 1939, complaining of pain in the right kidney region radiating to the right testicle of 4 days' duration and accompanied by passage of blood streaked urine. A left nephrolithomy was done in 1934. It was the patient's impression that several small concretions were left behind at the time of operation. He also gave a history of having passed a calculus from the right kidney prior to this operation and again following the operation. The postoperative course was complicated by a lung abscess which necessitated prolonged hospitalization. The patient stated that he was treated for gonorrhea 22 years previously.

Physical examination was essentially negative except for the right kidney which was palpable and exquisitely tender on percussion. The temperature was 104.2F, pulse 112, respiration 22, blood pressure 90/60. A plain urogram revealed the presence of an opaque shadow about 13 mm. long at the level of the transverse process of the third lumbar vertebra and numerous calcific shadows in the region of the left kidney. A 5F ureteral catheter was obstructed in the right ureter 3 cm. from the ureterovesical junction. With a little manipulation the obstruction was overcome and the catheter then ascended to the renal pelvis. Aspiration returned 17 cc of grossly clear urine.

A week later, when it was apparent that the calculus had not been expelled, and the pain in the right kidney area was still present, a 7F ureteral catheter was passed up the right ureter for a distance of 27 cm. Aspiration yielded 80 cc retained urine and showed innumerable white blood cells and a few red blood cells on microscopic examination. A right retrograde pyleogram indicated hydronephrosis with a suggestion of obstruction at the ureteropelvic junction and the calculus in the ureter in apposition to the catheter. The left pyelogram showed a normal architecture but contained numerous small calculi. The patient was admitted to the hospital. Excretory urograms confirmed the findings of the retrograde pyelograms. With a temperature rise to 105F, it was believed that an acute renal blockade was present and therefore, two 5F catheters were passed simultaneously into the renal pelvis. Aspiration now yielded only 5 cc of retained urine and the catheters were left indwelling. It was believed that some degree of impaction existed, since two previous ureteral catheterizations had failed to dislodge the stone. The temperature rise of 105F and the small amount of retained urine in the pelvis made us suspect that we were dealing with a cortical infection (multiple abscesses), the result of an ascending suppurative pyelonephritis.

The following day, under spinal anesthesia, the right ureter was exposed through a lumbar incision and the calculus extracted through a small incision directly over the stone. The opening was closed with two 00 chromic interrupted sutures, approximating the outer coats only. The kidney was then exposed. A large aberrant vessel was seen running across the ureteropelvic junction, although apparently causing no constriction. A marked amount of peri-ureteritis and peripyelitis was present. Just above the lower pole on its convex surface there was a carbuncle approximately 2.5 cm. in diameter. A culture from this lesion was positive for E. coli. The kidney was decapsulated and a rubber dam drain placed down to the carbuncle and another to the site of the incised ureter. The wound was closed in layers.

Pathological report: The specimen consisted of 3 fragments of a ureteral calculus, two of which were the size of half a pea, the other being 1.5 cm. long and 0.3 cm. in width. They were grayish-white and brown in color. Analysis was inadvertently omitted.

The postoperative course was uneventful and the patient was discharged after 15 days.

Case 2. A. S., a man 34 years of age, complained of pain in the right lumbar region of several days' duration. The patient stated he had noticed a small furuncle on his face 5 weeks prior to the onset of his illness, and had obtained pus by squeezing it. Excretory urograms at his physician's office proved unsatisfactory and he was admitted to the hospital for further study. There was no history of previous attacks and no other urinary symptoms. An appendectomy was done at the age of 9 and a pilonidal cyst removed at the age of 22. On admission, temperature was 99.2F, pulse 80, respiration 20, blood pressure 120/80. Physical findings were essentially negative except for some tenderness on percussion over the right kidney region. A plain urogram showed a suspicious shadow in the region of the ureteropelvic junction on the right. The bladder urine was grossly clear. The bladder appeared normal on cystoscopic examination. Indigo carmine injected intravenously appeared from the left ureteral orifice in 10 minutes in good concentration. No dye or urine was seen to emerge from the right orifice at the end of 15 minutes. A 6F catheter was passed up the right ureter where it was obstructed at 25 cm. On aspiration, 15 cc of retained urine were obtained. This was grossly clear and faintly blue-tinged at the end of 20 minutes. A 6F catheter ascended the left ureter for a distance of 27 cm. and met no obstruction. No retention of urine was discovered. Right and left retrograde pyelograms were now obtained separately. On withdrawal of the right catheter one had the impression that the catheter was tightly wedged against the calculus obstruction because of the amount of traction necessary.

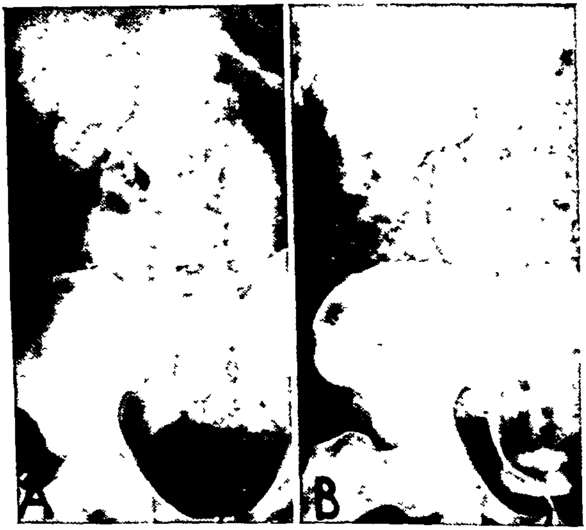

Fig. 1. *A*, right pyelogram showing filling defect in lower ureter (albumin stone). *B*, postoperative pyelogram subsequent to resection of kidney abscess.

Laboratory findings: Bladder urine: 2–3 white blood cells per high power field and 4–5 red blood cells per high power field; left kidney efflux: 1–2 red blood cells; right kidney efflux: 1–2 white blood cells and an occasional red blood cell. Cultures of all effluxes were positive for Pseudomonas aeruginosa. The blood count was normal.

Because of continued pain in the right kidney and failure to expel the calculus after 3 days, a 4F catheter was passed with difficulty beyond the calculus which was now situated 3 cm. above the ureterovesical junction (fig. 1, *A*). It was left indwelling for 24 hours. Following that cystoscopy, the patient experienced 2 chills and temperature rises to 105F. A blood culture was positive for Pseudomonas aeruginosa. It was not believed that we were dealing with a cortical infection (multiple abscesses) secondary to a bacteremia and suppurative pyelonephritis. Exploration of the right kidney was done 3 days later. Preliminary to operation, a 4F catheter was again passed up the right ureter for a distance of 23 cm. once more meeting the calculus at 3 cm. from the ureterovesical junction. A 5F catheter passed along side was completely blocked at this level. Both catheters were left indwelling while the patient was being prepared for surgery. Under spinal anesthesia, and by means of a right lumbar incision, the kidney was mobilized. The ureter just below the ureteropelvic junction was constricted by bands of adhesions as a result of peri-ureteritis. Perinephritis was also present, and on decapsulation, a carbuncle about 2.5 cm. in size was exposed on the convex surface in its midportion. The pelvis was opened and a clamp introduced coming out to the cortex and a nephrostomy tube placed in it through a nephrotomy incision. A 10F soft rubber splinting catheter was placed along side, brought through the pelvis, and down into the ureter to the junction of its middle and lower thirds. The lumbar incision was now extended anteriorly to expose the ureter in its lower third. The calculus in the ureter was extracted through a small incision in the ureter made directly over the stone. This calculus appeared to consist of organic material crumbling very easily (fibrin or albumin). The carbuncle was then excised with scalpel and cautery and the wedge packed with oxycel gauze. A rubber dam drain and gauze tamponade were now placed against the resected area and an additional rubber dam drain placed down to the opening of the ureter which was left open. The wound was then closed in layers. Pathological report: The specimen consisted of a triangular piece of tissue, pinkish, dark red and soft, measuring 1.5 by 1.5 by 1 cm. Separately received, there was a tiny fragment of pinkish material. Microscopic section through the larger section of tissue showed on one edge fairly normal kidney tissue. Most of the renal tissue was, however, diffusely infiltrated (polymorphonuclear leukocytes). The inflammatory process extended towards the kidney pelvis along all the removed kidney tissue. The original structure of the kidney could, however, still be recognized. Several extensive hemorrhagic areas also were present. The separately received pieces consisted of degenerated material. Definite structure could not be recognized. (However, this material was not received in fixative.) Diagnosis: Segment of kidney tissue showing severe, phlegmonous acute inflammation.

The postoperative course was complicated by the presence of bilateral bronchopneumonia which cleared up on streptomycin and penicillin therapy. The nephrostomy tube, splinting catheter and drains were removed on the fifth day and the patient was discharged 21 days after surgery. The urine cultures were still positive for Pseudomonas aeruginosa and, therefore, streptomycin was continued. Seven weeks later, because of markedly reduced function in the resected kidney (fig. 1, *B*), the presence of a draining urinary fistula and a grossly infected efflux on the same side, he was advised to return to the hospital at which time a subcapsular nephrectomy was done.

CONCLUSIONS

Two cases of carbuncle of the kidney, complicated by urinary calculi, are reported.

While the addition of the antibiotics to our armamentarium might reduce this clinical entity to a rarity, the presence of calculi or other obstructive uropathies may hinder effective action of these agents. Similar failures were reported when the sulfa compounds were hailed as the wonder drugs.

Conservative, rather than radical surgery, is probably the method of choice.

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REFERENCES

Brady, L.: International Clinics, **2**: 210, 1935.
Emmett, J. L. and Priestley, J. T.: Proc. Staff Meet. Mayo Clinic, **11**: 764, 1936.
Ingrish, G. A.: J. Urol., **42**: 326, 1939.
McNulty, T. H.: J. Urol., **35**: 15, 1936.
Mooney, K.: J. Urol., **47**: 249, 1942.
Nesbit, R. M. and Dick, V. S.: J. Urol., **43**: 623, 1940.

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PREGNANCY AND LABOR COMPLICATED BY PELVIC ECTOPIC KIDNEY

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In a previous review of the subject of pelvic ectopic kidneys complicated by pregnancy and labor,[1] the authors pointed out the scarcity of recent information available to the obstetrician in the proper management of such complications. After completion of the review, it became apparent from interviews and conversations that urologists were also unfamiliar with this particular problem of the ectopic kidney as a cause of dystocia or obstruction to normal labor. For this reason it seemed advisable to prepare a short report of our previous observations for a group of urologists.

The first case of a dystocia due to ectopic pelvic kidney was described by Hohl in 1928.[2] A pelvic mass described at delivery of 2 normal term infants was determined years later at autopsy to be a pelvic kidney. Since that time approximately 70 reports have appeared in the literature, most of which have been single case reports. However, in 1911, J. H. Girard[3] published a thesis at the University of Paris entitled, "L'ectopie simple congenitale du rein" in which he described 31 mothers having pelvic ectopic kidneys with a total of 109 pregnancies. Five of these cases had 13 abortions; and in 13 labors intervention was obligatory; 83 labors ended in spontaneous deliveries. Girard's monograph has been overlooked by many reporters on the subject of dystocia with ectopic pelvic kidney. Except for this monograph, most reviews have been incomplete. In a short paragraph Thompson and Pace who reviewed 88 cases of ectopic kidney at the Mayo Clinic, noted that 21 of their patients had been pregnant.[4] Fourteen of these mothers had one or more children without difficulty and 5 had one or more miscarriages and no full term infants. One woman had a stillborn at term, and another had her first child by a difficult forceps delivery and two children subsequently by cesarean section. Approximately 98 cases of pregnancy and labor complicated by pelvic ectopic kidney have been recorded in the literature between the years 1828–1948.[1] Certain essential facts on maternal and fetal outcome may be summarized as follows:

Number of mothers	98
Number of maternal deaths	10 (10.2%)
Total number of pregnancies in 98 mothers	226
Total number of abortions	35 (15.4%)
Number of premature infants	9 (3.9%)
Deaths of premature infants	4 (44.4%)

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Hot Springs, Va., March 23, 1950.

[1] Anderson, G. W., Rice, G. G. and Harris, B. A. Jr. Pregnancy and labor complicated by pelvic ectopic kidney anomalies. Obstetrical and Gynecological Survey, 4: 737–773, 1949.

[2] Hohl. Congenital pelvic kidney. Merkel's Archiv f. Anat. u. Physiol., 2: 177, 1928.

[3] Girard, J. H. Ectopic kidney. Inaugural Dissertation, Paris 1911. No. 439

[4] Thompson, G. J. and Pace, J. M.: Ectopic kidney. Surg., Gynec. & Obst., 64: 935, 1937.

Number of full term infants	182
Deaths of full term infants	28 (15.3%)
Deaths of viable infants	32 (16.7%)
Total fetal loss in 226 pregnancies (including abortions)	67 (29.6%)

From the above tabulation, the outstanding data are the 10 maternal deaths or a 10.2 per cent maternal mortality for 98 mothers. However, no maternal death due to pelvic kidney anomaly has occurred in the last 46 cases reported since 1927. Of the 10 deaths reported, 3 died of shock, 2 from infection, one each of eclampsia, ruptured uterus, and acute hemorrhagic nephritis. Two deaths were due to ill-advised procedures in the management of solitary kidney. In 1 case all the renal tissue of the patient was removed at the time of cesarean section.[5] In a second case partial nephrectomy was performed in an attempt to preserve some kidney cortex from infection without beneficial result.

Although the outlook for the mother with pelvic ectopic kidney anomalies has improved considerably, the fetal mortality remains between 14 and 16 per cent in the recently reported cases. The incidence of abortion (15.4 per cent) and prematurity are not increased over the normal frequency of these factors in the general population. In the 98 cases associated with pregnancy described in the literature, several different types of ectopia have occurred. These are illustrated in figure 1. They have been classified under a slight modification of that proposed by standard authorities such as Bell,[6] Everett[7] and Gutierrez.[8] Most of the cases (85) have been of the simple unilateral pelvic ectopia type. In 64 cases in which the exact kidney (right or left) was known, 86 per cent were left kidneys and 14 per cent were right kidneys. This compares with other studies on renal ectopia in the general population as follows:

AUTHOR	LEFT KIDNEY	RIGHT KIDNEY
Karschulin[9].	47 (71%)	19 (29%)
Bell[6]	18 (51.4%)	17 (48.6%)
Thompson and Pace[4].	40 (46%)	46 (54%)
Pregnant cases ...	55 (86%)	9 (14%)

The remaining 13 cases were of even greater interest since in 8 of these instances both of the kidneys were in the pelvis (3 were unfused and 5 cases were examples of horseshoe kidney or fused kidney) and the remaining 5 cases were solitary kidneys.

Crossed pelvic ectopia with or without fusion associated with pregnancy has not been recorded in the literature to the best of our knowledge. However, in a paper on crossed renal ectopia with fusion Wilmer[10] mentioned this possibility casually, but no specific references were quoted. In his review of crossed ectopia, Wilmer found 286 cases of unilateral fused kidney. He noted 2 cases in which the position and size of the renal mass offered an obstruction that necessitated cesarean section, but since exact details were not given these cases were not added to our review.

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[5] Idel, A.: Hydronephrosis of an ectopic fused kidney as an obstruction to delivery. Zentralbl. f. Gynak., 51: 2913, 1927.

[6] Bell, E. T. Renal Diseases. Philadelphia: Lea and Febiger, 1946.

[7] Everett, H.: Gynecological and Obstetrical Urology. Baltimore: Williams & Wilkins Co., 1948.

[8] Gutierrez, R.: The clinical management of horseshoe kidney. New York: Paul B. Hoeber Inc., 1944.

[9] Karschulin, O.: Observations on pelvic kidneys. Ztschr. f. urol. Chir., 34: 157, 1932.

[10] Wilmer, H. A.: Unilateral fused kidney: Report of 5 cases and review of the literature. J Urol , 40: 551, 1938.

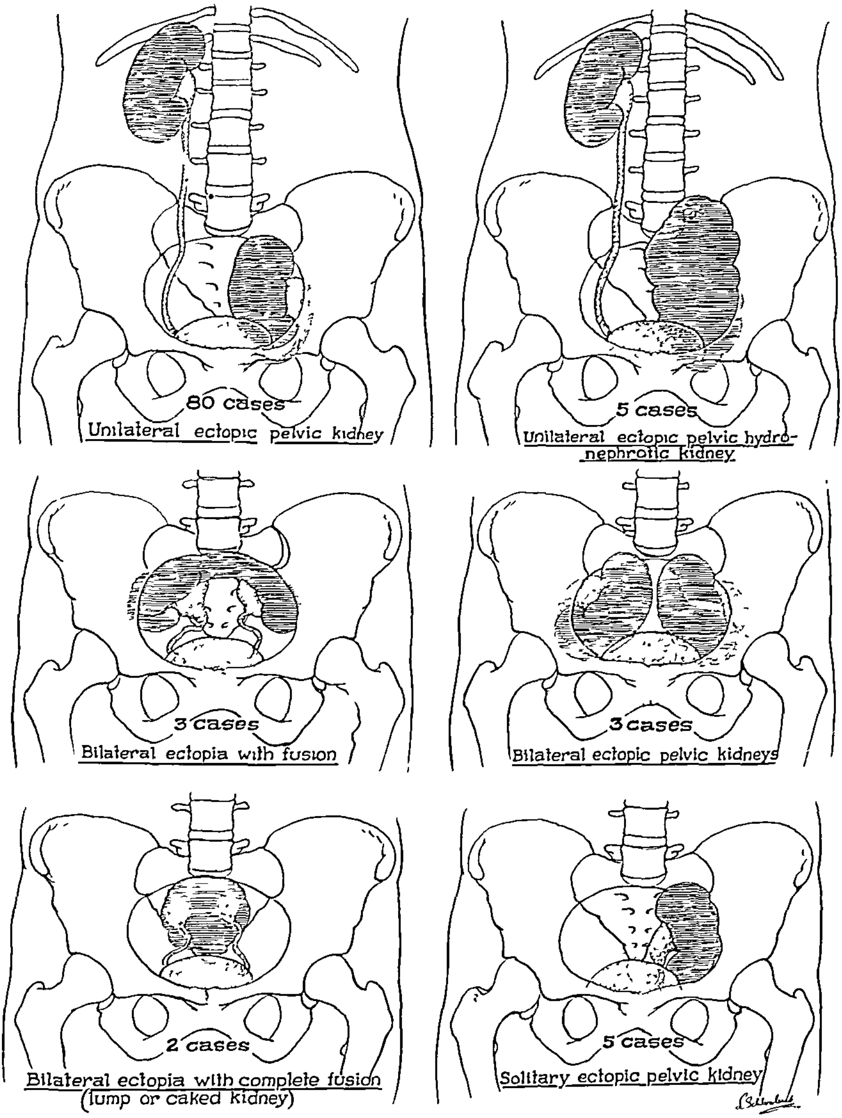
80 cases
Unilateral ectopic pelvic kidney
5 cases
Unilateral ectopic pelvic hydronephrotic kidney
3 cases
Bilateral ectopia with fusion
3 cases
Bilateral ectopic pelvic kidneys
2 cases
Bilateral ectopia with complete fusion (lump or caked kidney)
5 cases
Solitary ectopic pelvic kidney

Fig. 1. Diagrams showing various types and number of pelvic ectopic kidney anomalies associated with pregnancy observed in literature between 1828 and 1948.

Fitzgerald in 1940, after a very exhaustive search of the literature, concluded that his case of pelvic horseshoe kidney in a 19 year old primipara was the only recorded case of this particular type of pelvic ectopic kidney anomaly associated with pregnancy[11] This statement is not entirely accurate, since Bugbee and Losee[12] divided a pelvic horseshoe kidney in 1919 after the patient had 4 spontaneous labors Geinitz[13] in 1928 and Oliva[14] as early as 1898, described pelvic horseshoe kidney associated with pregnancy. Oliva's case is particularly interesting The patient entered the hospital with eclampsia, having convulsions. Her cervix was manually dilated and craniotomy performed on the infant. Both mother and baby died shortly thereafter. The horseshoe kidney was discovered at autopsy lying in the true pelvis.

Solitary pelvic kidneys have been described 5 times associated with pregnancy.[1] Two of the cases had eclampsia. In the third case, that of Fuchs[15] in 1938, cesarean hysterectomy was done to prevent future pregnancies. The fourth case of solitary kidney was observed by Ockerblad and Carlson[16] 6 years after 2 spontaneous labors with live full term infants. At death, only 40 grams of kidney tissue remained. In a fifth case, that of Dufour[17] the patient died 6 months postpartum following partial nephrectomy in an attempt to preserve the remaining kidney cortex from infection.

Among the many complications of pregnancy or of the kidney observed in 98 mothers the following may be listed:

	Cases
Very difficult labors	14
Nephrectomy during pregnancy	5
Hydronephrosis during pregnancy	5
Premature induction of labor	5
Postpartum pyelitis	5
Markedly contracted pelves	4
Sterilization for fear of future pregnancy and injury to the kidney	4
Adnexal anomalies—absence of tube or ovary on one side	3
Floating head at time of labor	3
Puncture of hydronephrosis at time of delivery	3
Eclampsia	2
Biopsy of pelvic mass to establish diagnosis of kidney	2
Bleeding into pelvic kidney	2
Spina bifida associated with pelvic ectopic kidney	1
Acute hemorrhagic nephritis	1

PRESENT STUDY

With the knowledge that only a few cases of ectopic pelvic kidney anomaly have been observed by any one obstetrician, it appeared beneficial to report

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[11] Fitzgerald L P Horseshoe kidney as a cause of dystocia J Missouri M A, **37:** 351, 1940

[12] Bugbee, H G and Losee, J R The clinical significance of congenital anomalies of the kidney and ureter Surg, Gynec & Obst, **28:** 97, 1919

[13] Geinitz, R Fused kidneys situated at the pelvic inlet and preventing normal birth Beitr z klin Chir **143:** 709, 1928

[14] Oliva, L A Puerperal eclampsia with a single kidney Boll R Acc Med Genova, **13:** 6, 1898

[15] Fuchs, H Pelvic kidney as an obstruction to delivery Zentralbl f Gynak, **62:** 1307 1938

[16] Ockerblad, N F and Carlson, H E Solitary pelvic ectopic kidney Brit J Surg, **12:** 43, 1950

[17] Dufour A Pelvic ectopia of the lower extremity of the left kidney Clin des Hop de Bruxelles, 1904

TABLE 1. *Cases of pelvic ectopic kidney anomalies and pregnancy delivered at the Johns Hopkins Hospital, 1927–1948*

CASE NO. YEAR	AGE	TIME OF DIAGNOSIS PRESENTING COMPLAINT	KIDNEY INVOLVED	NO. OF PREGNANCIES			METHOD OF DELIVERY	OUTCOME		REMARKS—FOLLOW-UP
				Abortions	Prematures	Full term		Baby	Mother	
U-15510 (1927)	35 (w)	After 4th pregnancy. Dx of ectopic preg. Exploration revealed pelvic kidney.	Left	1	0	5	4 spont. 1 breech	Alive	5 Alive	2 children died later of "flu". 2 children after Dx of pelvic kidney delivered spontaneously
103020 (1940)	30 (c)	Before pregnancy. Hypertensive toxemia. Pain: laparotomy	Right	1 Therapeutic	0	2	Spont. Spont.	Alive	Alive	Pelvic kidney removed because of hypertension: pathology report normal. 3rd preg. interrupted by hysterectomy because of only one remaining kidney. Lived 4 yrs. Died of hypertensive encephalopathy
238464 (1942)	19 (c)	During 2nd pregnancy. Possible ectopic preg. I.V. pyelography	Horseshoe	0	0	2	Forceps rotation C.S.	Alive	Alive	Difficult forceps, 1st delivery. Because of bil. pelvic kidney, C.S. was elected.
321078 (1944)	32 (c)	During 2nd pregnancy. "Ovarian tumor." Laparotomy	Left	1	0	1	Spont.	Alive	1 Alive	Laparotomy during preg. at 16 wks. followed 8 wks. later by 680 gm. abortion.

312626 (1915)	36 (c)	After pregnancy. Uterine myomas. Hysterectomy	Right	0	0	1	Spont.	Alive	Alive	Kidney located over pelvic brim. Might be described as iliac or pelvic ectopic kidney.
108583 (1917)	23 (w)	Before pregnancies. Pelvic mass (ovarian tumor). Laparotomy	Right	2	0	0	—	—	Alive	At operation absence of appendix also noted
111167 (1919)	18 (c)	Between pregnancies. Pelvic mass—ectopic pregnancy. Culdoscopy c̄ laparotomy	Left	0	0	2	Forceps Spont.	Alive Alive	Alive	Extensive condyloma acuminata during 1st pregnancy limiting pelvic exams. Successfully delivered 2 full term infants vaginally.

TABLE 1. *Cases of pelvic ectopic kidney anomalies and pregnancy delivered at the Johns Hopkins Hospital, 1927–1948*

CASE NO. YEAR	AGE	TIME OF DIAGNOSIS PRESENTING COMPLAINT	KIDNEY INVOLVED	NO. OF PREGNANCIES			METHOD OF DELIVERY	OUTCOME		REMARKS—FOLLOW-UP
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238461 (1942)	19 (c)	During 2nd pregnancy. Possible ectopic preg. I.V. pyelography	Horseshoe	0	0	2	Forceps rotation C. S.	Alive	Alive	Difficult forceps, 1st delivery. Because of bil. pelvic kidney, C.S. was elected.
321078 (1944)	32 (c)	During 2nd pregnancy. "Ovarian tumor." Laparotomy	Left	1	0	1	Spont.	Alive	1 Alive	Laparotomy during preg. at 16 wks. followed 8 wks. later by 680 gm. abortion.

342626 (1945)	36 (c)	After pregnancy. Uterine myomas. Hysterectomy	Right	0	0	1	Spont.	Alive	Alive	Kidney located over pelvic brim. Might be described as iliac or pelvic ectopic kidney.
408583 (1947)	23 (w)	Before pregnancies. Pelvic mass (ovarian tumor). Laparotomy	Right	2	0	0	—	—	Alive	At operation absence of appendix also noted
414167 (1949)	18 (c)	Between pregnancies. Pelvic mass—ectopic pregnancy. Culdoscopy c̄ laparotomy	Left	0	0	2	Forceps Spont.	Alive Alive	Alive	Extensive condyloma acuminata during 1st pregnancy limiting pelvic exams. Successfully delivered 2 full term infants vaginally.

TABLE 2. *Cases of pelvic ectopic kidney anomalies associated with pregnancy but delivery elsewhere—Johns Hopkins Hospital (1928–1949)*

CASE NO YEAR	AGE	TIME OF DIAGNOSIS, PRESENTING COMPLAINT	KIDNEY INVOLVED	NO. OF PREGNANCIES			METHOD OF DELIVERY	OUTCOME		REMARKS—FOLLOW UP
				Abortions	Prematures	Full term		Baby	Mother	
U-16274 (1928)	35 (w)	After pregnancies Tubo ovarian mass Pain laparotomy	Left	3	0	2	Forceps Forceps	Died 20th d Stillb.	Alive	Difficult forceps.
U-47727 (1933)	65 (w)	After pregnancies. Pelvic mass. Exploratory laparot	Right	1	0	7	All spont.	4 alive, 3 died of dis.	Alive	No difficulty c̄ deliveries. Some persistent urinary symptoms.
210191 (1940)	22 (w)	After pregnancy Pain in LLQ Nephrectomy Cystoscopy	Left	0	0	1	Spont.	Alive	Alive	Ectopic kidney c̄ hydronephrosis. Nephrectomy 3 yrs. after pregnancy
227919 (1941)	33 (w)	During pregnancy Hypertensive dis Kidney study	Right	1 Therapeutic	1	0	Cesarean section	Died	Alive	Both pregnancies terminated because of hypertensive disease
413512 (1947)	65 (w)	After pregnancies Urinary symptoms Left nephrectomy	Bilat	1	0	2	Spont.	Alive	Alive	Hydronephrosis developed in left kidney at 65 years of age. Left nephrectomy.
491701 (1949)	47 (w)	Long after pregs Medical work-up Cystoscopy	Right	1	0	1	Spont.	Alive	Alive	During attack of pneumonia and urinary infection approx 20 yrs. after pregnancies
502653 (1948)	34 (w)	After pregnancy	Right	0	0	1	Forceps	Alive	Alive	Developed hydronephrosis

our experiences with 14 additional cases. Seven cases of pregnancy complicated by pelvic ectopic kidney anomalies have occurred on the obstetrical service of The Johns Hopkins Hospital during the period 1927–1948. In this same period, 34,206 women were delivered, with an incidence of pelvic ectopic kidneys to deliveries of 1:4,886. This compares favorably with the reported incidence of pelvic ectopic kidneys in the general population. One of the cases (No. 238464) is a pelvic horseshoe kidney which is exceedingly rare and no comparable incidence rates have been published, but in our series it would be 1:34,206. The pertinent data on these 7 cases are shown in table 1. In addition to these, 7 cases of ectopic pelvic kidney observed by the urologic section of the gynecologic service of this hospital were also included in the study and data are recorded in table 2.

The maternal and fetal mortality of these 14 cases of pelvic kidney anomalies may be summarized as follows:

Number of mothers	14
Number of maternal deaths	0
Total number of pregnancies in 14 mothers	40
Total number of abortions	12 (30%)
Number of premature infants	1
Deaths of premature infants	1 (100%)
Number of full term infants	27
Deaths of full term infants	2 (7.4%)
Deaths of viable infants	3 (10.3%)
Total fetal loss in 40 pregnancies	15 (37.5%)

Analysis of this summary illustrates that maternal mortality is negligible during the period of pregnancy and the puerperium. One of the patients died 4 years after her last pregnancy of hypertensive disease. Her third pregnancy was terminated by hysterectomy because of the associated hypertensive toxemia. One other patient had 2 pregnancies interrupted for hypertensive toxemia; one by therapeutic abortion, and the second by cesarean section in which a premature infant (the only premature in the series) succumbed. The incidence of abortion (30 per cent) would be only 25 per cent if these 2 cases were deleted. The fetal mortality of 7.4 per cent for full term infants can also be reduced since, as the above tabulation illustrates, of 13 full term infants delivered in the Johns Hopkins Hospital all survived. The 2 deaths of full term infants occurred in another hospital following difficult forceps deliveries.

The method of delivery of the 27 full term infants and the fate of the babies may be summarized as follows:

METHOD OF DELIVERY	CASES	DEATHS
Spontaneous	20	0 (0%)
Forceps	5	2 (40%)
Breech	1	0
Cesarean section	1	0

The above data are significant since all of the cases except one were delivered vaginally. This exception was the only example of pelvic horseshoe kidney in the

14 cases studied. This case will be described in detail but it is interesting that the patient had been delivered of a previous child with what was described as a difficult forceps procedure.

In order to give the reader a more practical approach to the problem of pelvic renal ectopia associated with pregnancy 2 cases will be presented. The first case will illustrate the management of unilateral pelvic ectopia of the kidney during labor. The second case is an excellent example of the management of pelvic horseshoe kidney.

ILLUSTRATIVE CASES

Case 1. Unilateral pelvic ectopic kidney and management during labor. Mrs. L. H., No. 414167, a colored married woman 18 years of age, was first seen in the obstetrical dispensary on February 25, 1947. At this time, she was found to be 23 weeks' pregnant, complicated by extensive condylomata acuminata which filled the vaginal canal as a fungating, discharging, foul smelling mass. The patient was hospitalized on two occasions before delivery for penicillin and blood transfusion therapy in an attempt to control the vaginal infection. The patient resisted vaginal examinations and finally entered the hospital in labor and delivered a 3054 gm. male infant without difficulty. No one had any inkling of the kidney anomaly in this first pregnancy.

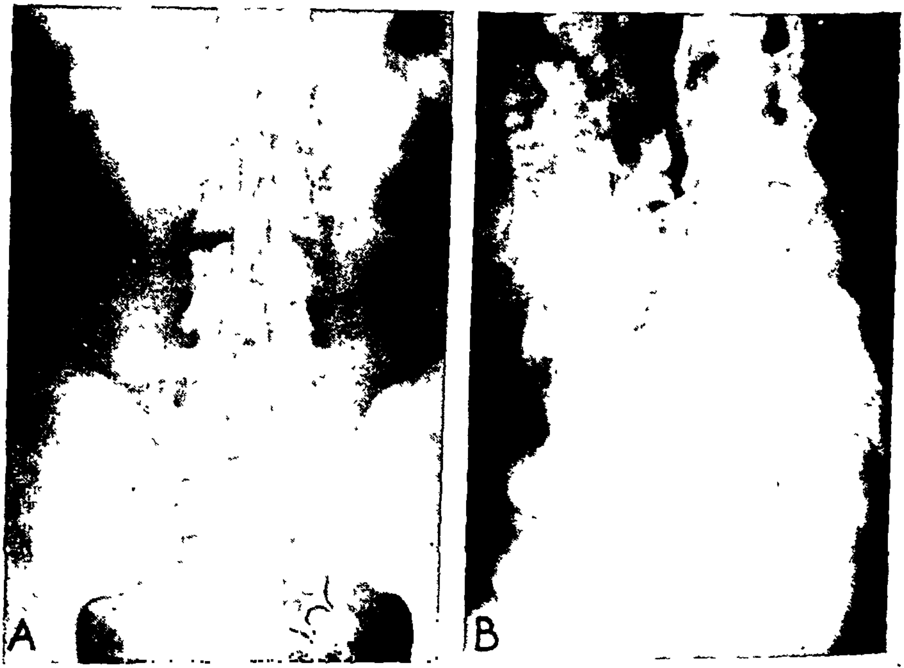


FIG. 2. Case 1. *A*, excretory urogram taken between pregnancies Right kidney in normal position while left kidney is in true pelvis *B*, excretory urogram taken 45 minutes before delivery. Kidney has ascended out of pelvis. At that point, kidney is still functioning and illustrates how kidney and fetal head accommodate to pelvic capacity (Films have been retouched to aid visualization for reader.)

One year later, March 15, 1948, the patient was examined in the obstetrical dispensary because of 4 months' amenorrhea. No pregnancy was present at this time but a 5 by 5 by 6 cm. mass was described in the left adnexal region. A presumptive diagnosis of ectopic pregnancy was made. On April 3, 1948, culdoscopy showed that the uterus, ovaries and tubes were not remarkable but a whitish mass covered by dilated blood vessels was observed in the cul-de-sac region. Laparotomy was performed revealing the mass to be a unilateral left pelvic ectopic kidney. The patient had an uneventful recovery and was subjected to excretory pyelography which revealed normal kidney outlines on the right and the calyces of the left kidney at the level of the first sacral vertebra. (fig. 2, *A*). On a subsequent visit to the cystoscopy clinic, retrograde pyelography was attempted on the left side but it was impossible to insert the catheter into the ureteral orifice on that side. Indigo carmine injected intravenously, however, appeared in the left ureteral orifice in 5 minutes, indicating good function in the left pelvic kidney.

The patient became pregnant shortly thereafter and registered for prenatal care on October 28, 1948. Her expected date of confinement was March 11, 1949. Her prenatal course was uneventful until March 10, 1949. On that date, the patient was admitted to the hospital because of slightly elevated blood pressure. Rectal examination revealed that the pelvic kidney could be felt distal to the head and extending down to the level of the ischial spines. On March 11, 1949, labor started. Sterile vaginal examination revealed the head of the baby to be only dipping into the true pelvis. X-ray pelvimetry revealed an adequate pelvic capacity. Prodromal labor followed for 24 hours, but by noon of March 12, 1949, labor pains were of good quality. By 5 p.m., the vertex had descended to the level of the ischial spines and the cervix was 3 cm. dilated. Catheterized urine examinations failed to show evidence of bleeding in the urinary tract. At this time the kidney was definitely movable and was not being compressed or wedged between the vertex and the sacrum. At 6:30 p.m., an excretory urogram was made and showed that the left kidney was functioning since the kidney pelvis was clearly outlined. (fig. 2, *B*). The patient returned to the delivery floor at 7:30 p.m. and at 7:50 p.m. her membranes spontaneously ruptured with the cervix 8 cm. dilated and the head on the perineal floor. Spontaneous delivery of a 3375 gm. female infant took place at 8 p.m., March 12, 1949. A small cervical laceration on the right side of the cervix was repaired. The left kidney was found to be located at the pelvic brim at completion of delivery. Catheterized urine drawn after delivery contained only 7 red blood cells per high power microscopic field. The patient's postpartum course was uneventful. The patient returned to cystoscopy 6 weeks later and urologic investigation was completely normal.

This case illustrates the mechanism by which a unilateral pelvic ectopic kidney can be bypassed by the vertex of the oncoming fetal head. This is illustrated in figure 3. The mechanism is similar to the action of labor in patients with fibromyomas located in the lower portion of the uterus, particularly as observed with cervical fibroids. Numerous vaginal examinations done during the course of the labor and the excretary pyelogram taken just before delivery support the mechanics of the diagram illustrated in figure 3.

Case 2. Bilateral pelvic ectopic kidney with fusion (pelvic horseshoe kidney). Mrs. V. G., No. 238464, a 19 year old colored married woman, was first seen in the obstetrical dispensary on September 16, 1941. At this time, she was 28 weeks' pregnant. No other findings were present at this time and the patient was registered as a normal primigravida. During her prenatal care, x-ray pelvimetry was obtained because of a breech presentation. The pelvic measurements revealed an adequate pelvic capacity. Her prenatal course was otherwise uneventful and on December 13, 1941 she was admitted to the delivery floor in active labor. Because of a "floating head" a sterile vaginal examination was done after 3 hours of labor. The cervix was 4 cm. dilated and a vertex with occiput posterior was presenting at a level of 2 cm. above the spines. The examiner felt a "rectosigmoid mass" which was not expected to cause serious dystocia. After 14 hours of hard labor the patient was delivered of an infant weighing 3690 gm., using Kielland forceps for rotation from occiput posterior to anterior position. This procedure was described as "quite difficult". The patient and her infant did well and were discharged in good condition.

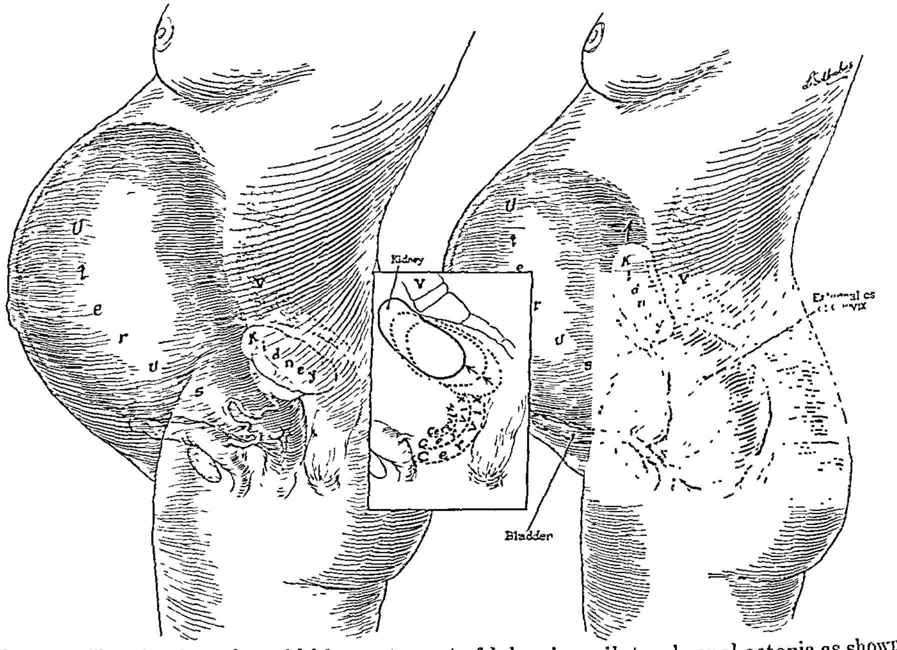
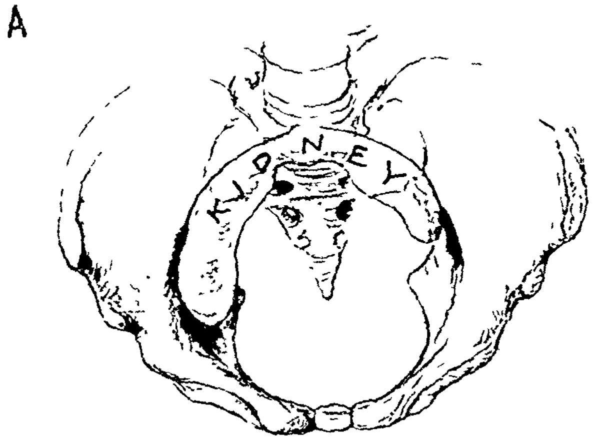


FIG. 3. Showing location of kidney at onset of labor in unilateral renal ectopia as shown on left, and subsequent ascent of kidney as fetal head descends deeper into pelvis during second stage of labor. Kidney also utilizes space laterally in both inlet and midplanes of bony pelvis.

On March 30, about 4 months after the delivery of the first infant, the patient was observed and followed by the gynecological service as a possible ectopic pregnancy, and finally on June 30, 1942, she was admitted to the hospital. Examination revealed a definite intrauterine pregnancy and also bilateral pelvic masses which were firm and nodular. At the suggestion of the senior gynecologist, excretory urography was performed and established the diagnosis of pelvic horseshoe kidney (fig. 4, *B*).



PELVIC HORSESHOE KIDNEY WITH PREGNANCY

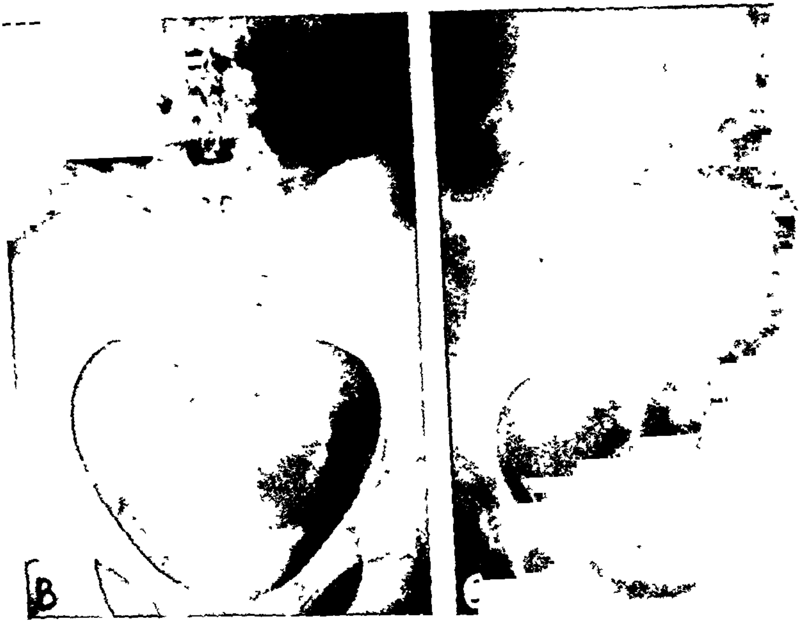


Fig. 4. Case 2. *A*, artist's concept of shape and location of bilateral fused ectopic pelvic kidneys at time of cesarean section. *B*, excretory pyelogram of a case of pelvic horseshoe kidney taken during third month of pregnancy. *C*, excretory pyelogram during ninth month of pregnancy showing vertex presentation of fetus. Compare ureters in *B* and *C*, which show very little of the dilatation usually associated with advanced stages of pregnancy.

The patient was then registered in the obstetrical clinic and allowed to continue with her pregnancy. There was considerable discussion as to the mode of delivery, but the previous difficult forceps and the possibility of injury to the kidney parenchyma decided in favor of cesarean section. Other x-rays were taken during pregnancy and resembled figure 4, *C*.

A low cervical cesarean section was performed and a 3460 gm. infant delivered without difficulty. On inspection of the pelvis following closure of the uterus, it was found that the horseshoe kidney extended about one-half to one inch above the sacral promontory and bulk of the kidneys extended over the sacrum and posterior pelvis for about 4 inches. Figure 4, *A* is an artist's drawing made at the time of cesarean section. The patient was also subjected to tubal resection at this time. The postoperative and postpartum course of the patient was uneventful. At the 6 weeks' examination, both urinary tract and genital tract were not remarkable.

This case illustrates that in order to make a diagnosis of pelvic kidney it is necessary that this possibility be kept in the obstetrician's mind and also illustrates that most pelvic kidneys will permit vaginal delivery. But it should also be pointed out that, with cases in which all of the kidney tissue is in the pelvis, it is probably wiser in this era of chemotherapy and safer cesarean section to consider abdominal delivery for this particular type of pelvic kidney.

DIAGNOSIS AND TREATMENT

Bell[6] describes the ectopic kidney as being subject to all diseases to which the normal kidney is liable with no increased incidence of any lesion except hydronephrosis and pyelonephritis. Pain is the usual presenting complaint in the nonpregnant cases of ectopic kidney, usually of the back or abdominal type of pain radiating to the hips and thighs. This usually accompanies the disease processes of hydronephrosis and pyelonephritis. Sometimes pressure on neighboring structures, such as the bladder, may produce hematuria and pyuria. Gutierrez[8] emphasized a symptom complex in horseshoe kidneys, consisting of pain about the epigastrium or umbilical region, history of chronic constipation with or without gastro-intestinal disturbances, and also urinary disturbances with early signs of chronic nephritis. Gutierrez[8] believes that the great majority of horseshoe kidneys are diseased but Bell[6] is not able to support this viewpoint. R. Bell[18] sent a questionnaire to members of the American Urological Association on the subject of horseshoe kidney and pregnancy. He received 286 replies. In this group, 96 women with horseshoe kidney had normal uneventful pregnancies. Forty-nine mothers went to full term but had some complication of pregnancy. Eight cases had labor induced. To the question "Do you consider horseshoe kidney a contraindication to pregnancy?" the vote was yes, 23; no, 117; and no opinion, 139.

In Thompson and Pace's[4] series of 88 patients with ectopic kidney 29 or 32.9 per cent suffered from recurrent attacks of pain. They believed that this was due to improper drainage of urine through the ureteropelvic juncture because of anomalous blood vessels and constricting bands of capsular and peripelvic tissue. These authors also pointed out that the pain in pelvic ectopic kidney would not necessarily be in the lumbar region but may be of a bizarre nature such as in one of their patients, a boxer by profession, who noted an indescribable sensation low in the abdomen whenever he skipped rope.

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[18] Bell, R.: Horseshoe kidney in pregnancy. J. Urol., 56: 159, 1946.

Since many patients with pelvic ectopic kidneys do not have symptoms, the diagnosis during pregnancy will depend largely on thorough pelvic examination in the early months of pregnancy. If pelvic masses or urinary symptoms are present, a complete urological survey of the patient, including urography, should be carried out. Unless the obstetrician has in mind the possibility of ectopic pelvic kidney very few cases will be diagnosed until the time of labor and delivery. Of 91 cases in the literature including 14 of the present study, on which accurate histories are available, the time of diagnosis in relation to the pregnancy may be summarized as follows:

	Cases	*Per cent*
Before pregnancy	4	(4.39)
During pregnancy	24	(26.36)
During labor	17	(18.68)
Immediate or late puerperium	8	(8.79)
Interval between pregnancies	8	(8.79)
Years after last pregnancy	23	(25.27)
At autopsy	7	(7.69)
Total	91	

It is notable that only 4.3 per cent of the cases were diagnosed before pregnancy; while 26 per cent were diagnosed by astute examiners during the pregnancy. Many of the cases diagnosed during pregnancy were seen during the second, third or fourth pregnancy and the examiner had the advantage of some history of either difficult labors or urinary tract symptoms following previous deliveries. Approximately 30 per cent of the cases were diagnosed years after the pregnancy or were discovered at autopsy.

Of the 24 cases diagnosed during pregnancy, 4 were originally confused with ectopic pregnancy. Four other cases were called ovarian cyst. Approximately 6 cases had peculiar sacral, lumbo-iliac or "bearing down" type of pain as the initial symptom. The remaining 10 cases were picked up by routine pelvic examination.

Seventeen cases were diagnosed during labor. Fourteen had painful and protracted labors which demanded further examination. In 3 cases the failure of the head to engage during active labor was the clinical point which attracted the attention of the examining physician.

Ectopic kidney in the nonpregnant patient usually requires no therapy unless symptoms are present due to definite underlying pathological changes. The experience of Thompson and Pace would justify this attitude.[4] In their series of 88 clinical cases treatment was confined to simple therapy of pyelonephritis. Twenty-one surgical procedures were carried out, but in many instances normal kidneys were removed. Such surgical procedures as treatment or urinary tract fistulas, neoplasms, tuberculosis, atrophy of the kidney, hydronephrosis, or removal of stones may be entirely justified in both nonpregnant and pregnant kidney parenchyma decided in favor of cesarean section. Other x-rays were taken during pregnancy and resembled figure 4, *C*.

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In 91 cases where data are available the following surgical procedures have been carried out:

	Cases
Sterilization	6
Nephrectomy during pregnancy ..	5
Nephrectomy after pregnancy..	5
Cesarean hysterectomy.	4
Puncture of pyonephrosis and hydronephrosis....	3

The decision as to the optimum type of delivery for the patient with labor complicated by pelvic ectopic kidney anomalies is not difficult at the present time in contrast to previous decades. Cesarean section can be judiciously employed in specific dystocia problems in which the pelvic kidney plays a major role. If the 182 full term deliveries reported in the previous literature are added to the 27 full term deliveries of the present study, 209 full term infants have been delivered in the following manner with their respective fetal mortality rates.

METHOD OF DELIVERY	CASES	FETAL DEATHS	PER CENT
Spontaneous	153	13	(8.4)
Forceps	6	3	(50)
Breech	11	5	(45.4)
Version and extraction	5	4	(80)
Cesarean section	32	3	(9.3)
Craniotomy	2	2	
Total	209	30	

From the foregoing tabulation it is apparent that a simple spontaneous delivery has about the same fetal mortality (8.4 per cent) as cesarean section (9.3 per cent) but if all deliveries from below are included (177 cases) then 27 infants were lost, a fetal mortality of 15.2 per cent. However, in 20 cases of full term deliveries in the authors' present study no fetal deaths occurred.

In 22 cases in which either bilateral pelvic ectopia with or without fusion or solitary kidney existed, in other words, all of the patient's renal tissue was located in the pelvis, the method of delivery was as follows:

METHOD OF DELIVERY	CASES	FETAL DEATHS
Spontaneous	15	0
Forceps	1	0
Cesarean section	5	0

It is apparent that delivery can be successful either by the vaginal or by the abdominal route if wise obstetrical decisions are made. Most cases of unilateral ectopic pelvic kidneys associated with pregnancy will deliver spontaneously provided the patient has an adequate pelvic capacity. This point should be checked not only by thorough clinical measurements but also by accurate x-ray pelvimetry. With adequate measurements of the diameters of inlet, midplane, and outlet planes of the true pelvis, the average sized child and normal sized kidney will compensate in the available pelvic space. This mechanism was readily demonstrated in our case 1. Frequent rectal and sterile vaginal examinations should be made during the course of labor to ascertain whether or not the kidney is being compressed against the sacrum as the baby's head advances. As long as the kidney possesses the mobility which was present at the onset of labor, it is apparent that the organ is not being subjected to abnormal pressure, which would in turn impede the forward progress or descent of the fetal head or injure the kidney parenchyma.

With bilateral pelvic ectopic kidney or solitary kidney, the obstetrician must remember that only 15 cases have been described in the world's literature.[1] Therefore, although 16 of 22 full term births have occurred vaginally, no chances should be taken. If vaginal delivery is decided upon in this type of pelvic renal ectopia the patient should make constant progress during her labor. Any abnormality, such as unengaged head at onset of labor, failure of hourly progress in descent, with progressive dilatation and effacement of the cervix, abnormal contraction patterns should be carefuly evaluated and abdominal delivery considered.

In consultation with the urologist, chemothrapy should be instituted for urinary infections, with dilatation and surgical removal of calculi in an effort to promote better renal drainage especially in those cases with hydronephrosis. In spite of these measures, the urologist in a few cases may have to advise nephrectomy, even during pregnancy.

One of the most important points to be brought out in this review is the danger of removing an unidentified pelvic mass either by the obstetrician at the time of cesarean section, or at subsequent laparotomy, only to find out that the removed tumor is a kidney. Foley and Wilmer[19] in a discussion on the surgery of unilateral fused kidney found 5 cases in the literature in which unthinking removal of the whole fused renal mass was, of course, followed by immediate death. Young also cites 12 deaths following nephrectomy performed on solitary single kidneys.[20]

SUMMARY

Our study included a review of 98 cases of pregnancy associated with pelvic kidney anomalies reported previously in the world's literature, and 14 additional cases observed in The Johns Hopkins Hospital during the years 1927 to 1948. The total number of pregnancies in the 98 mothers was 226, with an incidence of abortion of 15.4 per cent and a gross fetal mortality rate of 16.7 per cent. The fetal mortality rate for full term infants was 15.3 per cent and the maternal mortality was 10.2 per cent. Of the 14 patients in the present study, no mothers were lost and of 40 pregnancies, 12 ended in abortions, one in premature delivery, which infant died, and 27 full term infants with two infants (7.4 per cent) dead.

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[19] Foley, F. E. B. and Wilmer, H. A.: Surgery of the unilateral fused kidney. Surg., Gynec. & Obst., 70: 155, 1940.

[20] Young, H H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926, vol. 2, p. 11.

If the 14 cases of the present study are added to the 98 cases in the literature, a total of 112 cases of ectopic pelvic kidney anomalies associated with 209 full term deliveries have been recorded. Thirty infants died, a fetal mortality of 14.3 per cent.

The method of delivery in 209 full term deliveries was spontaneous in 153 (73.2 per cent), cesarean section in 32 (17 per cent), forceps, 6 cases; breech in 11 cases; version and extraction in 5 cases; and craniotomy in 2 cases. The fetal mortality was 8.4 per cent for spontaneous delivery as compared to 9.3 per cent for cesarean section.

Unilateral ectopic pelvic kidneys occurred once in 4,886 pregnant women while bilateral pelvic kidney occurred only once in 34,206 deliveries.

Various types of ectopic pelvic kidney anomalies associated with pregnancy may be summarized as follows: 1) simple unilateral pelvic renal ectopia, 97 cases in which 79 per cent have left kidneys and 21 per cent right kidneys; 2) bilateral pelvic renal ectopia, with or without fusion, 10 cases; 3) solitary pelvic kidneys, 5 cases.

The diagnosis and treatment during pregnancy depend upon thorough pelvic examination and investigation of pelvic masses. Such patients should be submitted to complete urologic investigation, including urography. X-ray pelvimetry is imperative to decide which patients have an adequate pelvic capacity for both kidney and the passage of the fetal head. The labor must be of an ideal type and continuous progress made, checked carefully by repeated vaginal examinations. During the labor the kidneys which possess any degree of mobility tend to rise out of the pelvis as the fetal head advances. Most women with ectopic pelvic kidneys may be delivered vaginally, but if all the renal tissue lies in the pelvis, such as in bilateral pelvic renal ectopia, or solitary kidneys, the wiser method of delivery would be elective cesarean section.

Pelvic ectopic kidney per se does not constitute an indication for interruption of pregnancy or sterilization. However, with supervening disease, such as intractable pyelitis, tuberculosis, hydronephrosis, neoplasm or toxemia, such procedures may be advisable.

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SUBCAPSULAR RENAL HEMORRHAGE CAUSING ANURIA OF SINGLE KIDNEY

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Mrs. M. Z., 44 years of age, married, mother of 3 children, was referred on April 21, 1942. In 1930 she had an episode of hematuria and cystoscopic study had disclosed an obstructed left ureter. For the past 3 years she had been under medical care for diabetes mellitus and about 6 weeks ago her physician found an elastic mass in the left upper quadrant. The bladder urine was acid, contained many leukocytes, erythrocytes, and acid fast bacilli. Excretory urography showed a large nonfunctioning left kidney, the right kidney showed good function but some pyelectasis. Cystoscopic examination with catheterization of the right ureter yielded clear urine, negative for tuberculosis by guinea pig inoculation. The left ureter presented an impassable obstruction at 3 cm. Medial to its meatus was a large area of fibrinous exudate. The diagnosis was therefore tuberculous pyonephrosis of left kidney, tuberculous stricture of left ureter and localized tuberculous cystitis. On May 9, 1942 aseptic left ureteronephrectomy[1] was performed (P. W. A.); the specimen confirmed the diagnosis. Both wounds healed per primam.

Despite control of the glycosuria, general supportive measures, and heliotherapy the bladder lesion proved very resistant. Leukocytes and erythrocytes persisted in the urine. On September 14, 1943, following cystoscopic examination, the patient failed to return for further observation until July 17, 1947. She now complained of suprapubic pain and the passage of blood clots. Cystoscopic inspection showed a massive, shaggy, white exudate on the left side of the bladder, the remainder presenting angry red mucosa, with bullous edema of the right ureteral orifice. Excretory urography showed good function of the remaining right kidney but its calyces, pelvis, and ureter were somewhat dilated. Again she disappeared from observation.

About a year later, August 31, 1948, she reappeared complaining of nocturnal incontinence of urine. On coughing, blood stained urine spurted from the urethra. A catheter yielded 6 ounces of urine, and a persistent mass in the pelvis proved to be an enlarged uterus. The right kidney was enlarged but not tender.

Excretory urography revealed delayed excretion and poor concentration of a hydronephrotic right kidney; its ureter was not portrayed. On cystoscopic inspection the entire bladder was covered with masses of shaggy exudate. She was again admitted, September 7, 1948, to the hospital. Blood urea nitrogen 18.3, uric acid 4.2, sugar 140, sedimentation rate 50 mm. in 1 hour. Streptomycin 0.25 gm. 4.i.d. was administered. After 2 weeks of preparation, a right cutaneous ureterostomy was performed under procaine spinal analgesia through a lower pararectus incision. The ureter was about 2½ cm. in diameter. The urine from it was clear and a guinea pig injected with it showed no evidence of tuberculosis. The kidney pelvis was drained by a No. 18 whistle tip catheter by way of the ureterostomy stoma. A persistent pyovesica required daily irrigation for several weeks. The ureterostomy drainage was maintained by a short tipped Foley (Wolf) catheter which was changed at regular intervals. The urinary bladder being thus excluded finally healed. Blood sugar was controlled, urea nitrogen 12.0. The patient was now comfortable and her general health steadily improving. She had been at home since October 3, 1948.

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[1] Aschner, P. W.: A technic of nephrectomy for tuberculosis, designed to prevent tuberculosis of the wound. Mount Sinai Hospital Bulletin, 4: 680, 1938.

On January 25, 1949 her temperature rose to 102F. The right kidney was very tender but not enlarged. The ureterostomy catheter was found encrusted when removed. A new one was inserted. A plain x-ray film showed no calculi. While dressing the patient had a chill and vomited.

Two days later her attending physician reported that at 6 p.m. (January 27) drainage had suddenly ceased although the output had been 1500 cc during the day. With that a mass had suddenly become apparent, tender and firm in the right kidney area.

She was promptly readmitted to the hospital. She was pallid, in severe pain. There was a large tender mass in the right kidney area; there was no drainage from the ureterostomy tube. The blood sugar was 410, urea nitrogen 38.0, CO_2 combining power 66 volumes per cent. Hemoglobin 65, red blood cells 3,370,000, white blood cells 16,650, polynuclears 76, band cells 10. Sedimentation rate 70 mm. in the hour.

It was my belief that there was obstruction at the ureteropelvic junction with an infected hydronephrosis. The catheter was removed, a new one passed but no urine was obtained. Still believing that we were dealing with obstruction, nephrostomy seemed indicated. Therefore under spinal hemianalgesia with Jones nupercaine solution and a transfusion going, a right lumbar incision was made. A large grayish lavender mass 20 by 13 by 10 cm. was exposed, apparently a greatly enlarged kidney. Attempted aspiration yielded only blood; not urine as was anticipated. The exposed thickened capsule was incised and a huge hematoma of fluid and clotted blood was evacuated. The kidney lay in the depth surrounded by adherent blood clot, which could readily be removed except at the middle third where the kidney tissue appeared granular. The capsule was completely incised, rubber dam placed in front and behind the exposed denuded organ and the wound closed. A fresh ureterostomy catheter was introduced. Within a few hours drainage was re-established or rather urinary excretion by the kidney resumed.

It was now evident that the anuria was not the result of obstruction but the result of compression or tamponade of the patient's solitary kidney by a massive subcapsular hematoma, the etiology of which was not as yet clear. The only clue was the area of granular tissue beneath adherent clot at the midconvexity of the organ. This could be an area of localized infection with infarction and hemorrhage. On the third day after surgery there was profuse urinary leakage from the wound, the dams were removed and the kidney inspected. The granular area noted above had necrosed and urine was coming through the defect. The wound became badly infected (Paracolon bacillus) and despite vigorous antidiabetic measures, transfusions, etc., the edges separated. Blood sugar declined to 240, urea nitrogen to 19.5. On February 21, 1949 the patient could return home. All drainage was through the ureterostomy tube.

The renal fistula had closed and the lumbar wound was granulating. Thereafter the lumbar wound healed completely and she has continued in comfort with proper care of her diabetes and of the ureterostomy tube, which is replaced readily at intervals of 4 to 6 weeks. Daily irrigation with Suby's G solution minimizes incrustation of the catheter.

DISCUSSION AND REVIEW OF LITERATURE

The history of this patient is of especial interest for several reasons. The previous left nephrectomy had made her completely dependent upon the remaining right kidney for excretory function and life. The persistence and subsequent aggravation of the vesical tuberculosis had necessitated ureterostomy to give relief from the bladder condition, and to protect the kidney from progressive obstructive and hydronephrotic destruction with its threat of uremia and death. The ureterostomy, however, subjected the remaining kidney to the dangers of ascending infection. It is reasonable to ascribe the temperature elevation and tenderness of the right kidney on January 25, 1949 to such an infection. The sudden cessation of urinary output with rapid "enlargement of the kidney" 2 days later were undoubtedly due to actual compression of the kidney by a huge subcapsular hematoma, reducing the pulse pressure in the organ below a level consistent with glomerular function and urinary excretion. One could, we believe, imitate this situation experimentally by applying an oncometer to the kidney (with nervous and vascular supply intact) and by increasing the extrarenal pressure enough to lower the pulse pressure within the organ sufficiently to stop urinary excretion.

As to the source of hemorrhage we cannot in this instance give positive proof but we may assume that the ascending infection resulted in a septic infarct of the kidney at the cortical area where the clot was found densely adherent, that a vessel in this area had sloughed and bled; that subsequently the slough separated resulting in a renal calyceal fistula as was observed postoperatively, and that eventually cicatrization and healing took place.

One of us (P. W. A.) had the opportunity to study the left kidney which he removed with capsule intact in a case of subcapsular hemorrhage.[2] Ureteral catheterization yielded no urine from this kidney before operation, whereas there was a fair flow from the right side. The specimen showed the whole kidney encased in a jelly like subcapsular mass 1.5 to 2 cm. in thickness. The upper pole presented a septic infarct (embolic) in which an arteria recta had ulcerated through the cortex and was the source of the subcapsular hemorrhage. A similar case was reported by K. A. Meyer.[3] When a subcapsular renal urinary fistula forms and persists, the lesion known as extrarenal hydronephrosis results. Interesting features of MacKenzie's case were the elevation of blood pressure noted preoperatively as the perirenal hematoma increased, and the elevated blood urea and a guinea pig injected with it showed no evidence of tuberculosis. The kidney pelvis was drained by a No. 18 whistle tip catheter by way of the ureterostomy stoma. A persistent pyovesica required daily irrigation for several weeks. The ureterostomy drainage was maintained by a short tipped Foley (Wolf) catheter which was changed at regular intervals. The urinary bladder being thus excluded finally healed. Blood sugar was controlled, urea nitrogen 12.0. The patient was now comfortable and her general health steadily improving. She had been at home since October 3, 1948.

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[2] Aschner, P. W.: Septic infarct of kidney, subcapsular hemorrhage. International Clinics 2 (series 33): 239, 1923.

[3] Meyer, K. A.: J. A. M. A., 72: 1451, 1919.

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FUSED PELVIC KIDNEYS

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Because of its appearance and shape, this rare type of anomaly is also referred to as "cake," "disc" and "shield" kidney. Kron and Meranze recently reviewed the literature and reported their case which is the seventh on record. Like all malformed kidneys, this particular type is naturally susceptible to infection. The patients whom we are reporting were both suffering from urosepsis; one was tuberculous and the other was an E. coli infection.

CASE REPORTS

A white laborer, aged 30, presented himself with a history of urinary frequency, burning and nocturia every half hour for the preceding 14 months. During this time he experienced several episodes of hematuria. Although he considered himself not very healthy, he had never been confined to bed because of illness and he had no previous hospital admissions. As far as he knew, there was no loss in weight.

No record of tuberculosis or cancer was uncovered in the family history. From the father, it was learned that the patient developed a spinal deformity in early childhood. He did not appear to be acutely ill and the body was deformed by kyphosis and scoliosis of the spine.

No active lesion was found in the chest on physical examination or roentgenologic study. The pulse rate was rather rapid (98) but the sounds and size of the heart were normal. The blood pressure was 124 systolic and 80 diastolic. Abdominal examination revealed nothing significant.

Laboratory reports: Kahn negative, blood urea 18 mg., 5,400,000 red blood cells and 16 mg. hemoglobin. The white cell count was 10,400 with 69 polynuclear forms, 28 small lymphocytes and 3 eosinophiles. Tubercle bacilli were found in the stained sediment from the left ureter and bladder. The specimen from the right side was negative for pus cells and bacteria. Guinea pig inoculation and culture were positive from the specimens other than from the right side.

Cystoscopy revealed extensive inflammation and limited bladder capacity. Retrograde studies showed the kidneys displaced downward into the bony pelvis and apparently in apposition. The right pyelogram was within normal limits and the left showed the typical moth eaten appearance of tuberculous invasion. Our diagnosis was bilateral pelvic kidneys with tuberculosis involving the left one.

After 3 weeks' preparation with streptomycin and rest, we decided to remove the left kidney. We were not aware of the renal fusion preoperatively.

Operation: The anesthetic was nitrous oxide and oxygen. Because of the deformity and the position of the kidneys, the incision was made from the border of the twelfth rib in the left flank downward and medially to the midline about two inches below the umbilicus. The peritoneum and contents were displaced medially without difficulty and the low lying kidney exposed. Mobilization was nitrogen.[4] His patient had polycythemia and the condition came on while he was chopping wood. The removed kidney showed no lesion.

A very complete review of the subject was given by Polkey and Vynalek in 1933[5] with an extensive bibliography appended. Of 200 cases 37 were subcapsular and 163 extracapsular hematomas. In 178 cases the etiology was as follows (no cases of trauma included in the study): diseases of the kidney 112 (63 per cent), of the suprarenals 11 (6 per cent); diseases of blood vessels 29.2 per cent, diseases of the blood 4.5 per cent such as: hemophilia, polycythemia, leukemia, scurvy, purpura, Hodgkin's disease; infectious 10 per cent, diseases of retroperitoneal tissues, no etiology given in 26 (14.6 per cent). The hematoma may rupture intra or extraperitoneally, it may resorb* or undergo organization. It may undergo cystic degeneration and become infected. The kidney may lie at the depth of the sac formed by its stretched capsule (hematonephrosis).

The striking clinical manifestations are abrupt onset with severe abdominal and flank pain, shock like symptoms, pallor and anemia. A mass was detected: 46 on the right, 59 on the left, and 6 bilaterally. Of 178 patients 98 died (56 per cent). In 62 nephrectomy was performed with 24 per cent mortality. *It is our belief that in many cases nephrectomy can be avoided.* When ruptured aneurysm of the renal artery or active bleeding from the kidney itself is found at operation its removal is usually necessary.

Additional individual case reports of perirenal hematoma since the comprehensive study of Polkey and Vynalek are cited in references.[6] We know of no other instance in which it has occurred about a single kidney, causing anuria. The recovery of our patient after decapsulation, evacuation and drainage indicates that a similar approach to the therapeutic problem in other instances could have avoided sacrifice of the kidney.

60 Plaza St., Brooklyn 17, N. Y.

[4] MacKenzie, D. V.: Perirenal hematoma primary with polycythemia. J. Urol. **23:** 535, 1930.

[5] Polkey, H. J. and Vynalek, W. J.: Spontaneous nontraumatic perirenal and renal hematomas, an experimental and clinical study. Arch. Surg., **26:** 196, 1933.

* Many years ago I explored a woman with a mass in the right upper quadrant. It proved to be a retroperitoneal hematoma surrounding the right kidney. The abdomen was closed without interference. The mass disappeared in two weeks. Subsequent cystoscopic and pyelographic study of the right kidney was negative (P.W.A.).

[6] Weaver, G. K. and Perry, I. H.: Periarteritis nodosa with fatal perirenal hemorrhage. J. A. M. A., **104:** 1390, 1935.

Counseller, V. S. and Emmett, J. L.: Left hematohydronephrosis with spontaneous rupture and perinephric hematoma. Proc. Staff Meet., Mayo Clinic **11:** 44, 1936.

Grauhan and Hellriegel: Massive hemorrhage perirenal due to renal sarcoma. Ztschr. f. Urol., **30:** 25, 1936.

Jasienski, G.: Spontaneous perirenal hematoma in a hemophiliac. J. d'urol., **44:** 487, 1937.

Price, C. W. R.: Retroperitoneal hemorrhage from angioma of kidney. Brit. Med. J., **2:** 831, 1940.

Irwin, F. G.: Spontaneous rupture of kidney. U. S. Navy Med. Bull., **41:** 818, 1943.

Longmire, W. P.: Perirenal hemorrhage from spontaneous rupture of intrarenal artery. J. Urol., **52:** 12, 1944.

Scrivner, W. S.: Intraabdominal hemorrhage of renal origin complicating pregnancy. Urol. and Cutan, Rev., **51:** 81, 1947.

Fort, C. A.: Spontaneous perirenal hematoma secondary to periarteritis nodosa. J. Urol., **59:** 307, 1948.

Miller, J. A. and Cordonnier, J. J. Perirenal hematoma associated with hypertension. J. Urol., **62:** 13, 1949.

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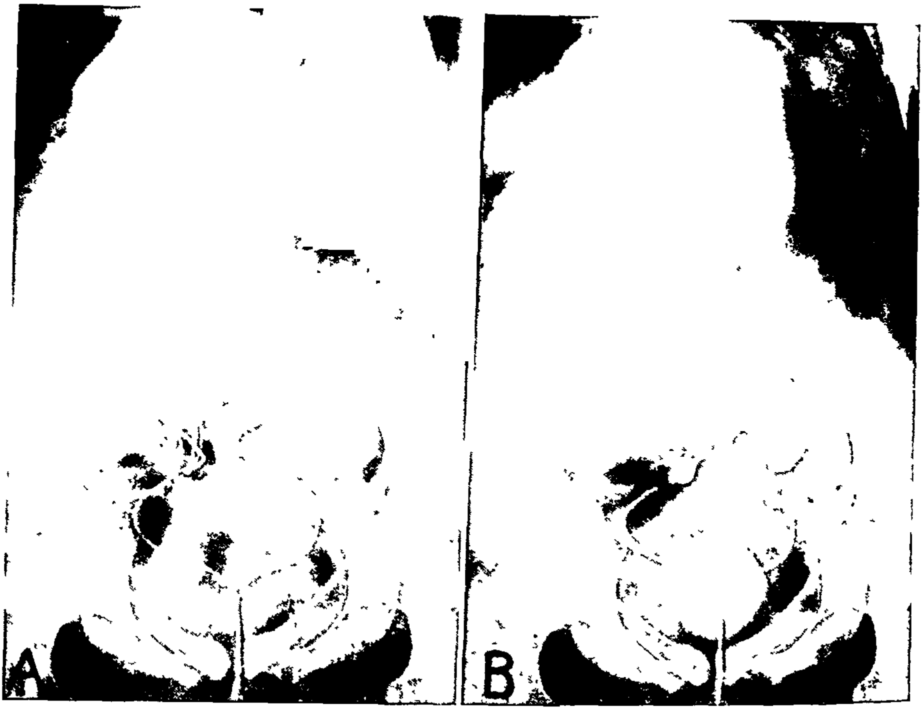

FIG. 1. *A*, plain film. Because of spinal deformity cardiac shadow appears in the study. *B*, retrograde study showing typical tuberculous involvement of right side

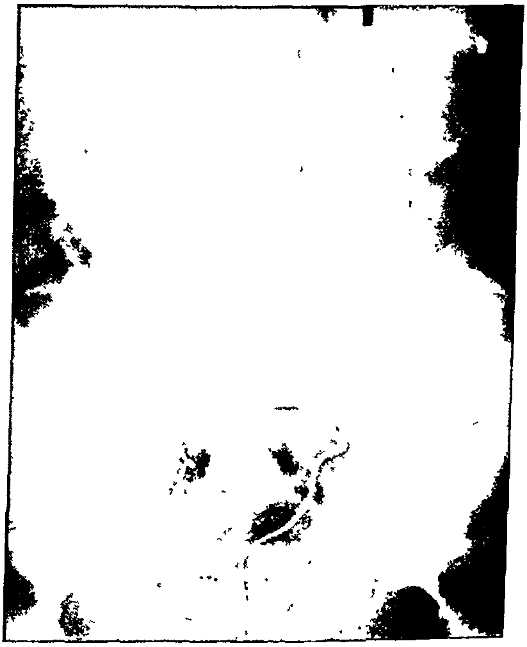

FIG. 2. Retrograde study of second case.

not difficult and at this point the fusion was discovered. The fused renal mass was divided in the midline and the incision closed with mattress sutures. Several abscessed areas were noted along the line of incision. The pedicle was handled in the usual manner and the incision closed without drainage. Operating time was 1 hour and 20 minutes.

Following operation, he appeared to react satisfactorily but only 50 cc urine was obtained during the first 24 hours. During the next 3 days, no urine was passed and he died on the fourth postoperative day.

Autopsy was permitted. The remaining right segment of the kidney measured 9 by 9 by 4 cm. and weighed 175 gm. The vascular pedicle had an adequate sized artery and vein. The adrenals were normal. The artery arose below the bifurcation. No other remarkable pathologic lesions were noted and there were no other congenital deformities.

Edema and bronchopneumonia were noted in the lungs and the kidney showed considerable parenchymatous degeneration. Microscopic section of the renal tissue showed a plugging of the tubules similar to that found in lower nephron nephrosis. The ureter was normal and unobstructed in its entire length. Although there was considerable round cell infiltration of the parenchyma, no definite tuberculous lesion was found in the right portion.

The specimen of kidney removed at operation measured 11 by 11 by 4 cm. and weighed 200 gm. Several large abscessed cavities were found containing a fairly large amount of pus. Microscopic sections showed numerous areas of degeneration and fibrosis. The typical epitheloid cells of tuberculosis and giant cells were noted in many of the sections. The diagnosis was tuberculosis of the right kidney.

The ureter was 9 cm. in length, indurated and the lumen was narrowed at two points.

The second patient was a 43 year old white laborer whose chief complaints were pain in the right lower quadrant, frequency and pyuria. He always enjoyed robust health and was never confined to bed with any illness.

After the usual careful physical examination we found nothing abnormal or remarkable. Cystoscopy was recommended and he submitted. The external genitals were normal and the cystoscope was introduced without difficulty. Microscopic examination of the urine specimen revealed numerous pus cells. The bladder mucosa was slightly congested throughout. Both ureters were catheterized without difficulty and no residual was noted on either side. The specimen from the left side was negative and the right revealed numerous pus cells. Bilateral retrograde study showed both renal pelves displaced downward to the bony pelvis and in fairly close apposition. The ureters were short and tortuous. The outline of the irregular renal shadow included both pyelograms. A urine culture yielded E. coli. After sulfonamide medication, the pyuria disappeared and the patient was symptom free.

SUMMARY

The eighth and ninth cases of fused pelvic kidney are added to the literature. The one patient died following an operation for the removal of the renal segment involved in tuberculosis and the other patient recovered from an E. coli infection under sulfonamide medication.

REFERENCE

Kron, S. D. and Meranze, D. R.: J. Urol., 61: 278, 1949.

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THE THORACO-ABDOMINAL INCISION IN UROLOGICAL SURGERY

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Since the deliberate employment of a thoraco-abdominal incision for the removal of kidney tumors was first reported[1, 2] about two years ago, this incision has come into constantly increasing use. Furthermore, increased experience with this approach has shown that, in addition to being of great value in the surgery of renal neoplasms, it is extremely advantageous in dealing with certain other conditions, and it is the purpose of this paper to call attention to the various uses of this incision in urological surgery. In addition to reports in the literature[3, 4] the author knows of various instances of its use here and there, but this communication will be based on the 68 cases in which the incision has been used by the author and by various of his colleagues at the Massachusetts General Hospital in Boston and the Veterans Administration Hospital in West Roxbury, Massachusetts.

Why is this incision finding increasing favor despite the fact that it is technically more complicated than an incision limited to the abdomen? The answer can be given in just three words: "superlatively good exposure." Since the diaphragm is frankly in the chest, and the kidneys lie to a considerable extent within the bony thorax and are sheltered by the lower ribs, it is a matter of common experience to have the unyielding bony thoracic cage interfere frequently with free and satisfactory exposure of the kidneys and the region immediately under the diaphragm when the usual lumbar approach is used. Even when the lumbar incision is made through the bed of the removed twelfth rib, or when the transperitoneal approach is used, there is often unsatisfactory surgical exposure of this region, especially when dealing with large kidney tumors. The thoraco-abdominal incision, by its approach directly through the chest and through the diaphragm, gives a magnificent wide exposure of just that area which is most difficult to expose by the other incisions, and that is why it is finding great favor. Particularly in the case of large kidney tumors, it has made their removal comparatively easy and safe instead of extremely difficult or even impossible, and for this advantage surgeons are glad to pay the price of employing this somewhat more complicated and time-consuming incision.

Undoubtedly the thoraco-abdominal incision's greatest value in urological

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 26, 1950.

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[1] Mortensen, H.: Transthoracic nephrectomy. J. Urol., 60: 855–858, 1948.

[2] Chute, R. and Soutter, L.: Thoraco-abdominal nephrectomy for large kidney tumors. J. Urol., 61: 688–696, 1949.

[3] Marshall, D. F. and Drake, E. H.: Transthoracic nephrectomy for metastatic osteogenic sarcoma of kidney. J. Urol., 62: 655–659, 1949.

[4] O'Conor, V. J. and Head, J. R.: Transthoracic nephrectomy (right) for tuberculosis of kidney. Surg., Gynec. & Obst., 89: 599–604, 1949.

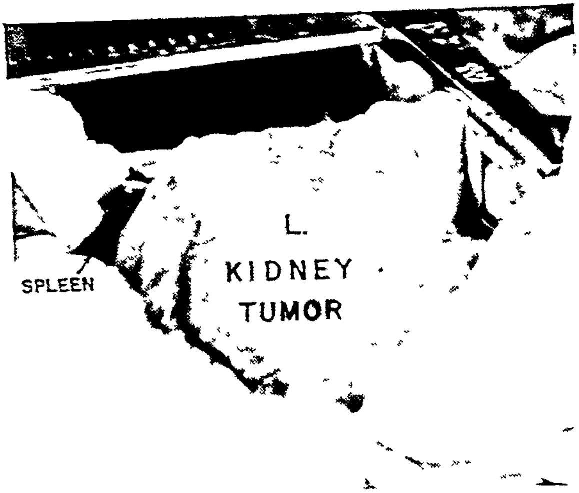

FIG. 1. Photograph taken at operation showing wound spread wide with rib retractor, and large tumor of left kidney bulging up into wound of its own accord. As yet, it has not been freed up at all. Spleen is packed away above. Patient living and well 3 years after operation.

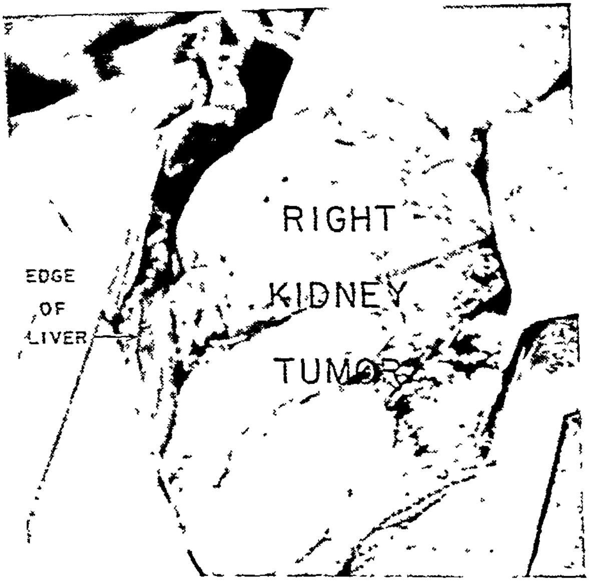

FIG. 2. Photograph taken at operation, showing wound spread wide with rib retractor, and huge tumor of right kidney (weight 1245 gm., 2.6 lbs.) presenting of its own accord. As yet it has not been freed up at all. Liver is easily retracted upward out of way. Patient living and well 25 months after operation.

surgery is in operations on renal tumors[5], of which there are 28 in this series. The wide open exposure gives a number of really important advantages: First, the vessels of the renal pedicle can without difficulty be discovered, exposed, and ligated under direct vision before the kidney has to be freed up (figs. 1 and 2). This greatly increases the ease and safety of the operation, and decreases the liability to accidents such as uncontrollable hemorrhage or injury to the inferior vena cava, which are usually the result of inadequate exposure and resulting imperfect visualization of important structures. Preliminary ligation of the renal pedicle makes the subsequent removal of the kidney tumor easy and bloodless. It also obviates the bothersome and sometimes dangerous hemorrhage from large veins which often course over the surface of some of these big tumors.

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[5] Chute, R., Soutter, L. and Kerr, W. S., Jr.: Value of thoraco-abdominal incision in removal of kidney tumors. New Eng. J. Med. 241: 951–960, 1949.

It seems very probable that some of the metastases which not infrequently follow the removal of malignant kidney tumors may be due to particles of tumor having been literally squeezed into the blood stream by the manipulations of the surgeon while freeing up a large tumor in order to get at its pedicle. Therefore, it would seem that early ligation of the pedicle before the kidney is manipulated or freed up cannot help but check that type of metastatic spread and thus improve the chances of cure. Another feature of the thoraco-abdominal incision is that the plane of cleavage naturally encountered is outside the perinephric fat and the capsule of Gerota, so that these are easily removed en bloc with the kidney (fig. 3). This is important when dealing with cancerous kidneys, as there may be direct extension of malignant disease to the perinephric fat. Room is also given for the removal of regional lymph nodes in the region of the pedicle and along the aorta and vena cava. This has been done in a number of the tumor cases, and many of the nodes have shown malignant involvement (fig. 4). Ample exposure is afforded to deal with unusual situations of which the following are examples: In several cases tumor thrombus has been found in the renal vein, and in one case the thrombus not only extended into the vena cava but had grown to its wall so that a portion of the wall had to be resected and then the cava sutured (fig. 5). Another tumor had involved part of the right lobe of the liver by direct extension, and it was possible to resect this and apparently get around the disease. In one case the vena cava was involved by direct extension of a right

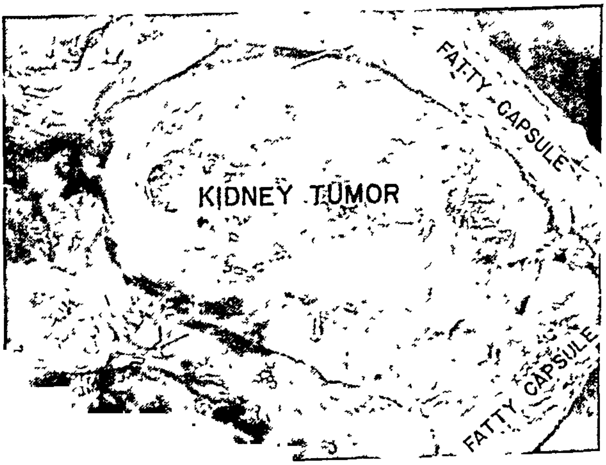

FIG. 3. Fatty capsule surrounding kidney tumor has been split to show its thickness Patient living and well 2 years after operation.

renal tumor about it and was ligated below the level of the left renal vein, and the involved section removed. It is significant that in 15 or more than half of the 28 cases of tumor, local extension was found at operation, and this figure would probably have been higher had not 2 of the tumors been rare benign ones,

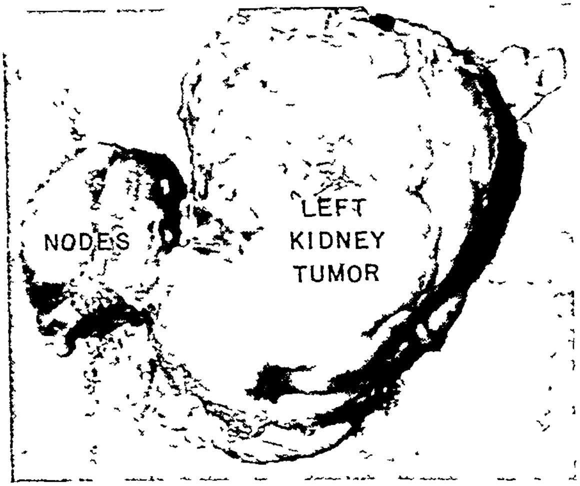

FIG. 4. Large tumor of left kidney (shown in figure 1) removed en bloc with attached metastatic nodes Note that all surrounding fatty capsule is removed with kidney. Patient living and well 3 years after operation.

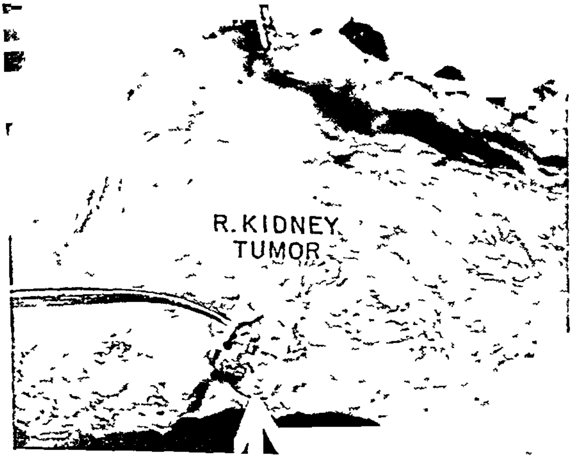

FIG. 5. Carcinoma of right kidney with tumor thrombus growing into inferior vena cava and adherent to it In order to remove thrombus, part of wall of vena cava had to be resected and sutured Patient living and well 2 years after operation White arrow points to tumor thrombus Hemostat is holding up renal vein and portion of vena cava.

one a cystic teratoma, the other a hamartoma. This means that the odds are in favor of discovering at operation some local extension, requiring more extensive surgery than simple nephrectomy. In such difficult cases the difference between success and failure may depend upon whether or not there is adequate exposure to carry out delicate and exacting surgical procedures. Therefore it is the opinion of the author and his colleagues that all kidney tumors, no matter what their size, should be operated upon by the thoraco-abdominal route, which gives adequate exposure, no matter how extensive the procedure. Thus in half of those cases with local extension, it was possible to remove all the obvious disease. As a corollary, it is not surprising that this incision has allowed the extirpation of large carcinomatous kidneys whose removal had been attempted by another approach but found impossible. In one of the cases, a large tumor whose removal had been attempted unsuccessfully by way of the lumbar route by an experienced surgeon, was later removed successfully by the same surgeon via the thoraco-abdominal route. In the opinion of the operating surgeons, at least 10 of these 28 tumor cases could not have been removed successfully through an incision giving less wide exposure. In this connection, it is significant, and an unusual record I believe, that in only one of our 28 cases of renal tumor, some of which were very large and adherent with local extension, was the kidney not removed. In this one case, widespread local extension of the malignant disease contraindicated any attempt at nephrectomy. Although it is the author's firm conviction that the surgical procedures made possible by the exposure afforded by the thoraco-abdominal incision will eventually be shown to increase the cures and lengthen the time of survival of patients with kidney tumors, the number of patients is too small and the follow-up period too short to allow any conclusions of value to be reached at the present time. However the figures are as follows: Sixteen of the 28 tumor cases, including the first patient operated upon in January 1948, who had involved lymph nodes excised en bloc with his renal carcinoma, are living and apparently well of their disease. (Among these are 6 whose follow-up period has been exceedingly short, as they were operated on in recent months.) Four are living with metastases which were seen at the time of operation. Six patients, all but one of whom were seen to have metastases at the time of operation, have died of their disease. There was one postoperative death, and one patient never returned for follow-up after his operation.

Since tumors of the adrenal gland are situated high up under the diaphragm above the kidneys, the surgical approach to them is even more hindered by the ribs, and their exposure by the usual approaches is even less satisfactory than is the case with kidney tumors. As in the case of the latter, it has been found that the thoraco-abdominal incision affords excellent direct exposure of the adrenal region—definitely better than that obtained by any other approach. The urological staff of the hospitals where the author does his work does not do the surgery of adrenal tumors, and therefore the author has had no personal experience in such cases. However, he can definitely state that the surgeons who do operate on adrenal tumors at these hospitals have found the thoraco-abdominal incision so satisfactory that they have been using it routinely for about two years in cases of adrenal hyperplasia in heavily built persons, and for all adrenal tumors in adults, except pheochromocytomas. In the case of pheochromocytomas, since they may be multiple and scattered, and so much variation is possible in their location, it is believed that an abdominal incision usually gives the best opportunity to explore the region of the adrenals and the abdomen with a view to removing any pheochromocytomas discovered. However, if the pheochromocytoma is seen in the x-ray film to be in the usual position of the adrenal, the thoraco-abdominal incision might be used. About 12 adrenal operations have been done using this approach with very satisfactory results. These are in addition to the 68 urological cases upon which this report is based.

A situation in which the thoraco-abdominal incision is indispensable is in cases where the kidney should be removed but where due to the bony deformity of extreme kyphosis or scoliosis the rib cage makes an impassable barrier to the usual type of lumbar approach. Two such cases have been encountered and operated upon successfully. One was a woman of 68 who had a large pyonephrotic kidney on the left that was giving her symptoms. She also had a marked rotoscoliosis concave to the left making the usual lumbar approach out of the question (fig. 6, *A*). She was operated on thoraco-abdominally and the large pyonephrotic kidney removed. In addition, there was a perinephric abscess. With the aid of antibiotics, the wound healed without significant sepsis. The second case was more extreme. The patient was a woman of 35 who had had tuberculosis of the spine as a child with resulting extreme kyphosis. Five years previously hematuria, frequency, dysuria, and urgency had appeared. and it was found that she had tuberculosis of her right kidney, while the other kidney

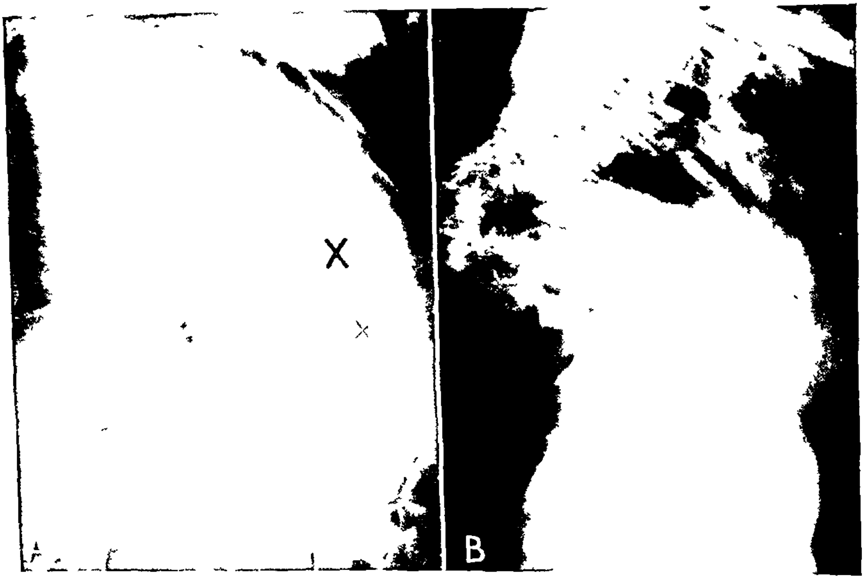

FIG. 6. *A*, patient with marked rotoscoliosis. Thoraco-abdominal nephrectomy for pyonephrosis and perinephric abscess on left (marked X). Wound healed without significant sepsis *B*, patient with extreme kyphosis. Poor anesthetic risk because of very low vital capacity Tuberculous right kidney causing severe bladder symptoms removed thoraco-abdominally without trouble. Excellent convalescence.

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Since tumors of the adrenal gland are situated high up under the diaphragm above the kidneys, the surgical approach to them is even more hindered by the ribs, and their exposure by the usual approaches is even less satisfactory than is the case with kidney tumors. As in the case of the latter, it has been found that the thoraco-abdominal incision affords excellent direct exposure of the adrenal region—definitely better than that obtained by any other approach. The urological staff of the hospitals where the author does his work does not do the surgery of adrenal tumors, and therefore the author has had no personal experience in such cases. However, he can definitely state that the surgeons who do operate on adrenal tumors at these hospitals have found the thoraco-abdominal incision so satisfactory that they have been using it routinely for about two years in cases of adrenal hyperplasia in heavily built persons, and for all adrenal tumors in adults, except pheochromocytomas. In the case of pheochromocytomas, since they may be multiple and scattered, and so much variation is possible in their location, it is believed that an abdominal incision usually gives the best opportunity to explore the region of the adrenals and the abdomen with a view to removing any pheochromocytomas discovered. However, if the pheochromocytoma is seen in the x-ray film to be in the usual position of the adrenal, the thoraco-abdominal incision might be used. About 12 adrenal operations have been done using this approach with very satisfactory results. These are in addition to the 68 urological cases upon which this report is based.

A situation in which the thoraco-abdominal incision is indispensable is in cases where the kidney should be removed but where due to the bony deformity of extreme kyphosis or scoliosis the rib cage makes an impassable barrier to the usual type of lumbar approach. Two such cases have been encountered and operated upon successfully. One was a woman of 68 who had a large pyonephrotic kidney on the left that was giving her symptoms. She also had a marked rotoscoliosis concave to the left making the usual lumbar approach out of the question (fig. 6, *A*). She was operated on thoraco-abdominally and the large pyonephrotic kidney removed. In addition, there was a perinephric abscess. With the aid of antibiotics, the wound healed without significant sepsis. The second case was more extreme. The patient was a woman of 35 who had had tuberculosis of the spine as a child with resulting extreme kyphosis. Five years previously hematuria, frequency, dysuria, and urgency had appeared, and it was found that she had tuberculosis of her right kidney, while the other kidney

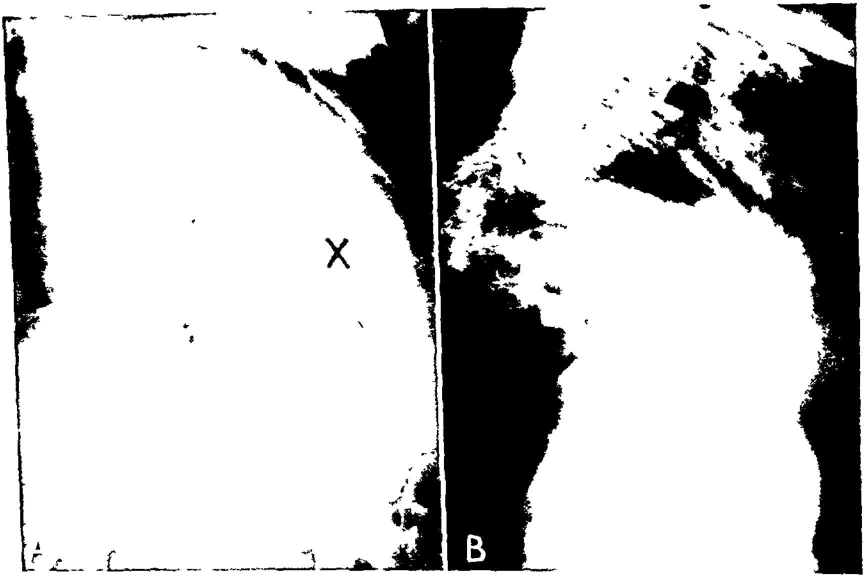

FIG. 6. *A*, patient with marked rotoscoliosis. Thoraco-abdominal nephrectomy for pyonephrosis and perinephric abscess on left (marked X). Wound healed without significant sepsis. *B*, patient with extreme kyphosis. Poor anesthetic risk because of very low vital capacity Tuberculous right kidney causing severe bladder symptoms removed thoraco-abdominally without trouble. Excellent convalescence.

was normal. She had been seen by two excellent urologists who felt that nephrectomy was out of the question on account of her kyphosis (fig. 6, *B*), and she had been relegated to a sanatorium life. Because of exacerbation of her urinary symptoms, her case was reviewed and, although she was considered a poor anesthetic risk due to her very low vital capacity, thoraco-abdominal nephrectomy was carried out successfully. She made an excellent recovery.

A fourth condition in which the thoraco-abdominal approach has been found to be markedly advantageous is in performing retroperitoneal dissections to remove lymph node metastases from carcinoma of the testis.[6] The lymphatics from the testes accompany the spermatic vessels upward to the general region of the renal pedicle and the aorta and vena cava at that level. This is the area of the embryological development of the testes, and there is evidence indicating that this region is the primary site of lymphatic metastases from carcinoma of the testis. Secondary lymphatic spread of the malignant disease across the midline, down along the large vessels to the iliacs, and also above is frequently seen. Without going into a discussion of the various types of malignant testicular tumors, and in which types and situations lymphadenectomy is indicated, suffice it to say that when retroperitoneal node dissection is indicated, experience with the thoraco-abdominal approach on 7 occasions has shown it to be definitely superior for this purpose to other types of surgical

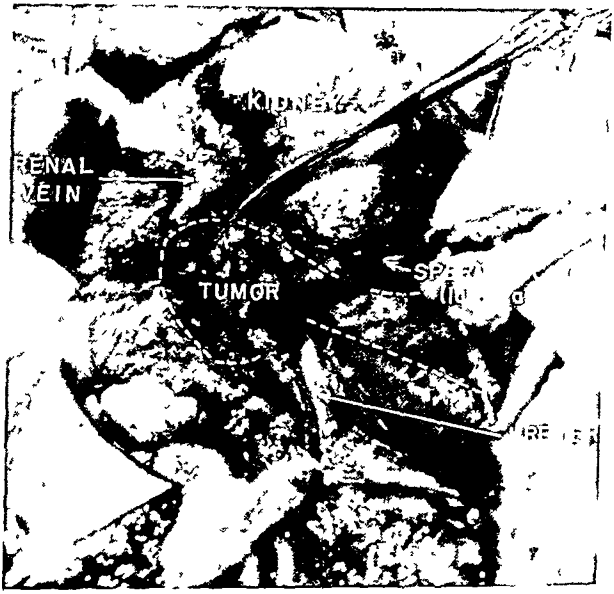

FIG. 7. Retroperitoneal dissection (left) for metastases from carcinoma of left testis Thoraco-abdominal incision used. Note excellent exposure of region of renal pedicle and great vessels. Hemostat is pointing to large mass of tumor tissue (indicated by dotted line) at upper end of spermatic vessels just below renal vein. Tumor incased aorta and infiltrated left psoas muscle, and was inoperable.

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[6] Cooper, J. F., Leadbetter, W F. and Chute, R.: The thoraco-abdominal approach for retroperitoneal gland dissection: Its application to testis tumors Surg, Gynec & Obst, 90: 486–496, 1950.

approach, such as transforming the upper end of the incision into a lumbar kidney incision, as it gives far better access to and exposure of the region of the renal pedicle, and above it up to the diaphragm (fig. 7). The thoraco-abdominal incision in the region of the tenth rib is extended obliquely downward lateral to the rectus muscle into the lower quadrant of the abdomen toward the pubic bone to permit the dissection of the lower abdominal and pelvic lymph nodes.

Another important use for the thoraco-abdominal approach is to facilitate nephrectomy in cases of chronic calculous pyelonephritis or pyonephrosis. Such cases are apt to have dense perinephric fibrous adhesions which make surgery very difficult indeed, especially in those cases previously operated on, which are notorious for dense scar formation. In such cases, the thoraco-abdominal incision, by giving a very wide exposure, has allowed the pedicle to be approached and secured from the anterior-medial aspect facing the peritoneal cavity where adhesions and scar tissue are apt to be either minimal or absent. Following the ligation of the pedicle, the kidney can be dissected out carefully without bleeding. Nephrectomy has been performed on 8 such difficult cases with satisfaction and success. Four of the 8 had had a previous attempt by a competent surgeon at removal of the kidney through a lumbar incision, but these attempts had been unsuccessful because the kidneys were so "stuck." Because of continuance of bothersome symptoms, including pain, and depression of their general condition, it was decided to try to remove their kidneys thoraco-abdominally, and this was accomplished successfully.

DISCUSSION

In this series of 68 thoraco-abdominal urological operations, which does not include the dozen thoraco-abdominal adrenal operations, the incision was performed 36 times on the left and 32 times on the right. On the right side, the liver has always been easily retracted upward, so that it has never been in the way, even in one case where it was moderately enlarged.

The patients varied in age from 1 year (a baby boy with a large cystic teratoma) to 80 years, and 7 patients were over 70. Despite the fact that several patients had cardiac disease, there were no postoperative cardiac complications, except for 1 woman of 77 whose heart decompensated temporarily 1 week after operation. There were no pneumonic complications, no pulmonary emboli, and no chest or peritoneal infections. With the exception of the one death and 3 complications about to be described, the postoperative recoveries were uneventful, and the length of the postoperative stay in the hospital was the same as for uncomplicated lumbar nephrectomies.

As already mentioned, there was 1 death, and 3 complications, 2 of which were from intrapleural hemorrhage, due to the operator's failure to secure adequate hemostasis. The first complication due to intrapleural bleeding was minor in nature, the chest clearing after one thoracentesis. In the second case of intrapleural hemorrhage, persistent bleeding into the chest, probably from torn pulmonary adhesions, necessitated several thoracenteses, as well as blood transfusions, during the first few days after operation. Eventually the blood in the chest became so thick and clotted that it could not be removed, and it bound down and collapsed the lower and middle lobes of the right lung, making an open surgical decortication necessary. The patient, who was 75 years of age, tolerated this procedure well and went home in good condition. The third complication was more serious. The patient was an extremely obese woman of 48 who had been known to have severe arterial hypertension for at least 15 years. Her blood pressure on entry into the hospital was 250/160, and a cardiac consultant considered her only a fair operative risk. She tolerated nephrectomy well, but the evening after operation had a sudden fall in blood pressure to about 80 systolic without signs of hemorrhage. The blood pressure was successfully raised with a blood transfusion and intravenous fluids in a short time, and did not fall again. However on the third postoperative day, she developed right hemiplegia which a neurological consultant thought was due to an infarct in the region of the pons. After 2 weeks, during which time there was no obvious improvement, she was discharged to a hospital for chronic care. This was a month ago. The one death occurred in the fifty-first case. The patient was a man of 62 who had a renal cell carcinoma of the right kidney with a tumor thrombus in the renal vein. The kidney and the renal vein containing the thrombus were removed, but in so doing the vena cava was torn with resulting profuse hemorrhage. Rather than suture the vena cava, the operator elected to ligate it, believing the upper point of ligation to be below the entrance of the left renal vein into the vena cava. Postoperatively the patient suffered from prolonged hypotension with the systolic blood pressure never rising above 80, despite stimulating drugs and replacement by transfusions of more than the amount of blood lost. During the 3 days that this patient lived, there was practically no urinary output. Permission for postmortem examination was not obtained, so the exact cause of death was not ascertained.

Twenty-one cases were operated upon as kidney tumor "suspects" but no tumor was found. These were mostly cases of large solitary cysts, indistinguishable by x-ray from kidney tumors, but there were a few cases where there was some bizarre deformity of the pyelogram strongly suggesting tumor. In a number of these cases nephrectomy was performed, but in cases with obvious cysts, the cysts were merely saucerized.

In discussing the thoraco-abdominal incision, the author has sometimes heard urological surgeons say that, while they admitted that the exposure obtained was phenomenally good, they were a little hesitant about entering the chest and going through the pleural cavity and the diaphragm, feeling that this made the operation complicated technically and might lead to chest complications, and also increase the risk and the shock of the operation. In answer, the author can only say that, although opening and especially closing the chest must be done carefully, the technique is perfectly simple, and can be learned from operating a few times with a thoracic surgeon. The 2 cases of intrapleural hemorrhage in this series were attributable to preventable technical failure to secure proper hemostasis before closing the chest. They occurred rather early in the series, and there have not been any chest complications in the last 50 cases. As to operative shock, with well-trained anesthetists giving intratracheal ether-oxygen anesthesia, and by taking care not to lag behind in replacing blood loss by transfusions, it has been the experience of the author and his colleagues that shock is minimal, and does not occur at all in the average case. Despite the fact that, in some of the more complicated cases, the operation has lasted several hours and considerable blood has been lost, the element of shock has almost always been surprisingly minimal. The 68 cases in this series were done by 11 different operators, about one quarter of the total having been operated upon by the resident house staff.

SUMMARY

The thoraco-abdominal incision is of great value in certain types of cases in urological surgery (68 cases of author and colleagues).

Its value lies in the remarkably wide open exposure of the infra-diaphragmatic area and the region of the kidney and the adrenal which it affords.

Undoubtedly this incision's greatest usefulness is in the removal of kidney tumors (28 cases). The author feels strongly that the thoraco-abdominal incision should always be used in operating on all kidney tumor cases for the following reasons:

The renal pedicle is ligated more easily and thus more safely.

Preliminary ligation of the renal pedicle before freeing up the kidney blocks the escape of metastases, and makes the tumor's subsequent removal easy and bloodless. Also it eliminates the frequently bothersome hemorrhage from large veins on the surface of the tumor.

The surrounding perinephric fat and capsule of Gerota are removed easily en bloc with the kidney. It is important to do this as they may be involved by direct extension of the malignant disease.

There is plenty of room and exposure to make possible: a) removal of involved regional lymph nodes, b) removal of tumor thrombi from the renal vein or the vena cava, c) any other difficult surgery which may be necessary in order to remove local extension of the disease (e.g. a portion of one lobe of the liver involved by direct extension was removed in 1 case).

The incision has made possible the removal of kidney tumors considered inoperable when approached by the conventional lumbar kidney incision.

At operation, local extension of the malignant disease was found in 54 per cent of the 28 cases, and in half of these cases it was possible to remove the obvious local extension by surgery, which was sometimes quite difficult. In view of this 54 per cent probability of local extension which may require surgery more complicated than nephrectomy alone, the operator must prepare for possible extensive surgery by using that incision giving the widest exposure obtainable.

Although the number of patients is too small and the follow-up period is too short to allow any conclusions of value at the present time, it is the author's firm conviction that the surgical procedures made possible by this exposure will eventually be shown to increase the cures and lengthen the time of survival of patients with kidney tumors.

It has been found that tumors of the adrenal in the adult, except for pheochromocytomas, are best exposed and dealt with by means of a thoraco-abdominal incision (about 12 cases in addition to the 68 urological cases). Pheochromocytomas, because of the wide variation possible in their location, are probably best searched for through an abdominal incision, unless they are seen by x-ray to be in the usual position of the adrenal.

This incision makes nephrectomy possible in cases of extreme scoliosis or kyphosis (2 cases).

For retroperitoneal node dissection in metastatic carcinoma of the testis, the thoraco-abdominal incision gives the best exposure of any incision for dissection in the region of the renal pedicle, the primary site of metastasis (7 cases).

The thoraco-abdominal approach greatly facilitates nephrectomy in difficult cases of calculus pyelonephritis or pyonephrosis (6 cases).

The patients varied in age from 1 year to 80 years. The operation was performed 36 times on the left and 32 times on the right.

In this series of 68 thoraco-abdominal operations, one death occurred in a man of 62 who had his vena cava ligated because of operative trauma and hemorrhage. During the 3 days he lived, his blood pressure was low and he excreted very little urine. Postmortem examination was not done. There were three complications: 1) right hemiplegia on the third postoperative day in a severe hypertensive, blood pressure 250/160; 2) gross and persistent hemorrhage into the pleural cavity requiring thoracenteses, transfusions, and eventually a decortication of the lung; 3) a small intrapleural hemorrhage which cleared up after one thoracentesis. There were no other complications.

With the exception of the one death and the two most serious complications, all the patients did very well postoperatively, and the length of their stay in the hospital was the same as for uncomplicated lumbar nephrectomy.

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URETERAL MEATOTOMY WITH THE FINE-WIRE ELECTRODE

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A fine-wire electrode of the kind known as the Timberlake or the Hyams has been found very useful in performing ureteral meatotomy.

The fine wire is extruded from the insulating sheath to a distance exactly equal to the desired length of the meatotomy incision. Using a McCarthy panendoscope, the wire is thrust into the ureter as far as it will go, the end of the insulating sheath acting as a stop. The outer end of the panendoscope is then greatly depressed, so that the electrode pries the ureteral ridge up toward the dome of the bladder and places it under tension. The bladder is well filled with water so that no other part of its wall will be injured. The cutting current is set at a point almost as high as for transurethral resection, so that a quick, clean and bloodless cut will be made. A momentary touch on the foot switch produces a clean, bloodless cut of the same length as the extruded portion of

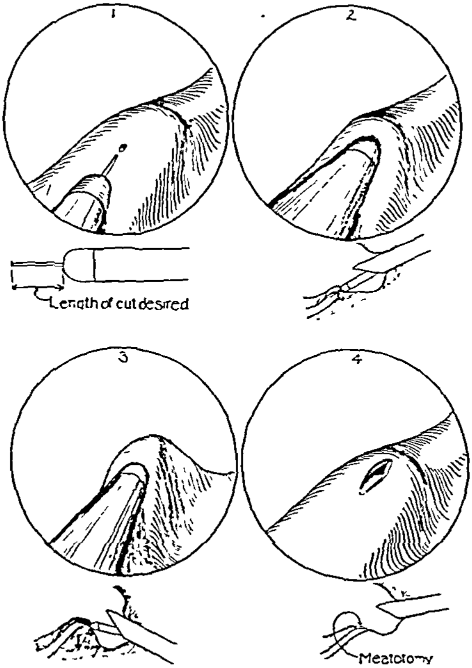

FIG. 1. *1*, Electrode ready to be inserted in small ureteral orifice. Diagram below shows how length of cut is determined by length of wire left exposed. *2*, Electrode thrust into ureter as far as it will go, insulating sheath acting as a stop. *3*, Ocular end of panendoscope being depressed, ureteral ridge is pried up, bringing wire in close contact with roof of ureter. *4*, After cutting current is turned on, ureteral ridge falls away from electrode, leaving clean, bloodless cut exactly same length as exposed segment of wire.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

the wire, the ureteral ridge falling away from the electrode automatically and back to its normal position.

The advantages of this method appear to me as follows: 1) no special apparatus is required; 2) the exact length of the cut can be determined beforehand, and it is practically impossible for it to be made any longer, thus avoiding all danger of extravasation; and 3) there is no bleeding.

The method has been in use in my clinic for more than ten years, with great satisfaction, and appears to be as nearly fool proof as any urological procedure can be.

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PRIMARY CARCINOMA OF THE URETER

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Primary carcinoma of the ureter, which is being reported with increasing frequency, still is an interesting and rare condition. Long, in a review of the literature in 1949, found 201 cases and added one more.[1] Since then Brooks has reported 3 cases.[2] Two cases are being reported here.

OCCURRENCE

According to Anderson, they make up 1 per cent of the tumors of the upper urinary tract. They occur in the lower third of the ureter in 75 per cent of the cases.[3] They have a tendency to be multiple.

PATHOLOGY

Melicow added considerably to our knowledge of these tumors and their behavior when he called attention to the fact that, embryologically and histologically, the linings of the pelvis, ureter, and bladder are similar.[4] Because the mucosa was impervious to urine, he called it urothelium to distinguish between the skin and lining of the gastro-intestinal tract. Neoplasms from any point along this urothelium have similar gross and microscopic pictures. Structurally, they may be papillary, sessile, or polypoid—the papillary group composing 75 per cent of the total, and about 60 per cent of this group are malignant. There is a definite tendency for multiplicity along the urothelium,[5] and this may have been erroneously called tendency to recur. This multiplicity was first thought to be an implantation by surface extension, but this seems to have been disproved. The second theory was extension by lymphatic spread. Histologically, the lymphatics are especially numerous in the stroma of the ureter, which corresponds to the submucosa. This would lead one to believe that a lymphatic spread would be plausible,[6] but according to Sakata the lymphatics of the ureter fall into three groups: 1) an upper group, which joins the renal lymphatics;[7] 2) a middle group which drains into the interiliac nodes; and 3) a lower group, which anastomose with the lymphatics of the bladder. This division of lymphatics would disprove such a theory, and one would expect to see more growths in the lower ureter secondary to bladder tumors. A lymphatic spread could well explain the case of Ferris, in which growths in the lowermost portion of both ureters appeared secondary to a bladder tumor.[8] Vesical tumors, however, rarely are accompanied by tumors in the upper urinary tract. Thirdly, there is a

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

[1] Long, J. H.: J. Urol., 61: 23, 1949.

[2] Brooks, W. H.: J. Urol., 61: 29, 1949.

[3] Anderson, W.A.D.: Pathology. St. Louis: C. V. Mosby, 1948.

[4] Melicow, M. M.: J. Urol., 54: 186, 1945.

[5] Bailey, M. K., Fort, C. A. and Harlin, H. C.: J. Urol., 62: 44, 1949.

[6] Smith, E. P. and Copenhaver, W. M.: Bailey's Textbook of Histology. Baltimore: Williams and Wilkins, 1948, 12th ed.

[7] Morris: Human Anatomy. Philadelphia: Blakiston, 1942.

[8] Ferris, D. O., Kaplan, J. H. and Thompson, G. J.: J. Urol., 62: 448, 1949.

multicentric origin described by Ewing which postulates that different parts of the urothelium have the same carcinogenetic properties.[9] The primary carcinomas of the ureter are often associated with calculi. They metastasize early and more extensively than carcinoma of the bladder, and may involve the regional nodes, liver, vertebrae, lung, kidney, spleen, brain, pancreas, skin, pericardium, and prostate.[3]

ETIOLOGY

The most interesting aspect of carcinoma of the ureter is its etiology or pathogenesis. Much has been written on this subject both from the experimental and clinical viewpoint. Cullough and Doldorf, according to Fagerstrom, were able to produce metaplasia in animals with a diet deficient in vitamin A and with overdoses of sex hormones.[10] This metaplasia was nullified by feeding vitamin A. Bothe made serial sections of 6 ureters removed for carcinoma, both adjacent to the growth and in the distal portions.[11] From his pathologic studies, he concluded that papillary carcinoma of the ureter was caused by excretory irritants or more probably carcinogenic agents which reached the ureter through the blood or lymph. He also deducted that implantation was not the cause of all the lesions. Anderson believes that it is "doubtful if leukoplakia ever developed into malignant neoplasm of the ureter".[3]

Fagerstrom proved that there was no basis for the cell nest theory of Von Brunn,[9] and believed that the etiology was carcinogenic. Gualteri, in a discussion of the pathogenesis of these tumors,[12] believes that they were initiated with carcinogens and perpetrated by tissue enzymes. Hughes showed that homologous transplants of bladder mucosa in direct contact with the carcinogen-20-methyl cholanthrene, which is the most active carcinogen today, produced epithelial tumors.[13] This carcinogenic agent is found in the sex hormones, which in turn are all derived from cholesterol, and in folic acid. This carcinogenic theory seems to be the most plausible one, and if urine-borne, explains the reported disappearance of bladder carcinoma following diversion of the urinary stream, but does not explain why tumors continue to appear in the ureter following nephrectomy for papillary carcinoma of the pelvis. If this carcinogenic agent is brought to the urothelium through the blood or lymph, it is surprising that one does not find tumors in the opposite ureter as well as on the same side as the initial lesion.

SYMPTOMS

The symptoms of primary carcinoma of the ureter are hematuria in about 75 per cent of the cases, protruding tumor in about 25 per cent of the cases, and the rest of the symptoms are due to ureteral obstruction.[14]

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[9] Ewing, J.: Neoplastic Diseases. Philadelphia: W. B. Saunders Co.

[10] Fagerstrom, D. P.: J. Urol., **59**: 333, 1948.

[11] Bothe, A. E.: J. Urol., **49**: 69, 1943.

[12] Gualteri, T., Hayes, J. J. and Segal, A. D.: J. Urol., **59**: 1083, 1948.

[13] Hughes, B.: J. Urol., **62**: 833, 1949.

[14] Harrison, F. G., Warres, H. L. and Fust, J. A.: Ann. Surg., **130**: 902, 1949.

CASE REPORTS

Case 1. W. L. G., a 60-year-old white man, was first seen on July 8, 1947, complaining of pain in his left side, with hematuria. Cystoscopic examination revealed an obstruction in the lower left ureter which was proved to be a ureteral calculus. Excretary urograms showed distention of the ureter and kidney on that side behind the obstruction. A small calculus was passed after a ureteral meatotomy.

Two months later a follow-up cystoscopic examination showed no obstruction, and a left pyelogram showed a return of the kidney to normal size and architecture. A good ureterogram was not obtained at this time. See figure 1.

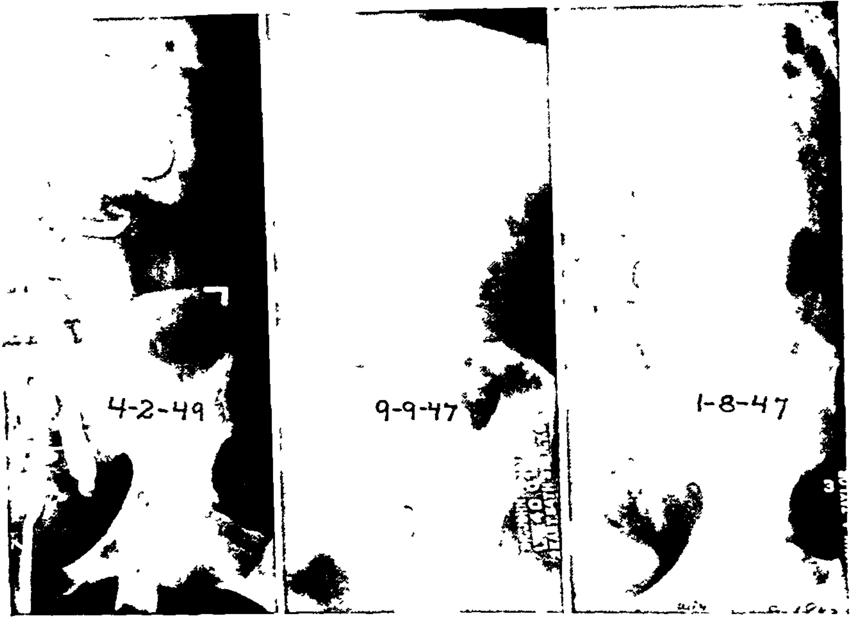

FIG. 1

On March 22, 1949, the patient complained of painless hematuria of 5 days' duration. Cystoscopic examination showed a small papillomatous growth projecting from the left ureteral orifice. He was admitted to St. Luke's Hospital on April 1, 1949, for a biopsy and preoperative workup. A small piece of the papillomatous growth was biopsied, and the biopsy showed "only a mass of hyalinized connective tissue with a few small blood vessels and a few muscle cells. No malignant cells are seen. The small size of the biopsy specimen makes diagnosis unsatisfactory."

Both ureters were catheterized, and phenolsulfonphthalein was obtained from the right kidney after intravenous injection in 3 minutes, and was markedly delayed on the left. X-ray studies showed a normal right urinary tract, with left hydro-ureter and hydronephrosis, with a filling defect in the lowermost portion of the left ureter. Urine was obtained for cytologic study, and was sent to Dr.

Papanicolaou. It was reported: "Urine specimen of April 5, 1949, fairly good evidence of malignant neoplasm, class 4."

General physical examination was essentially negative, with a blood pressure of 164/78. The only abnormal findings were a left oblique inguinal hernia and an enlarged left kidney. X-ray of the chest showed no evidence of metastasis. Urea nitrogen was 13.5, sugar 102, and CO_2 54.1. An electrocardiogram showed normal rhythm.

On April 20, 1949, a left nephro-ureterectomy was done, the kidney and upper part of the ureter being removed first through a lumbar incision, and the lower ureter through a left paramedian incision. In removing the lower part of the ureter, which was very edematous and friable, it was accidentally torn. In order to insure complete removal of the growth, which was in the lowermost portion of the ureter, the bladder was opened, and the incision was carried down to and around the left ureteral orifice, which had a catheter in situ. After a good cuff of the bladder was resected, it was clamped off and the lowermost portion of the ureter was freed through the bladder. The resection of the ureter was then completed from above. The incision in the bladder was closed around a Pezzer catheter. The patient received 500 cc blood and returned to his room in good condition, and had an uneventful convalescence.

The pathological report (Dr. B. Earl Clarke) was as follows:

"Gross description: Specimen consists of the left kidney weighing 107 gm. and measuring 11 by 5.5 by 3 cm..... The calyces extend to within 5 mm. of the surface and in no renal pyramids are recognizable. The renal pelvis is lined by smooth, shiny, opaque mucosa and the wall is thin....

"Received separately are two segments of ureter. At the lower end of the longer segment there arises from the mucosa a firm, papillary and nodular tumor, 1.8 cm. in diameter. In this area the external surface of the ureter is smooth and its wall is soft. For a distance of 1.5 cm. above the tumor the mucosa is opaque, indurated and raised 1 mm. in height. The remaining portions have a soft wall and a smooth. shiny, opaque mucosa.

"Microscopic description (fig. 2): Sections of the kidney reveal considerable interstitial fibrosis and infiltration by lymphocytes and plasma cells....

"A portion of renal pelvis is seen lined by intact, normal appearing transitional epithelium.

"The section of ureter in the region of the tumor shows a superficial tumor composed of orderly arranged, solid groups of spindle and cuboidal cells. closely packed and quite uniform in size and shape. Mitotic figures are rare. The tumor is grossly papillary in some areas but in most areas consists of solid groups of tumor separated by thin strands of connective tissue.

"The base shows the origin of the tumor from normal appearing transitional epithelium and the tumor shows no microscopic evidence of invasion of the muscular coats of the ureter.

"Diagnosis: Carcinoma of the left ureter (transitional cell type); left hydronephrosis, chronic pyelonephritis."

Case 2. T. D., a 74-year-old woman, was first seen on June 1, 1949. She gave

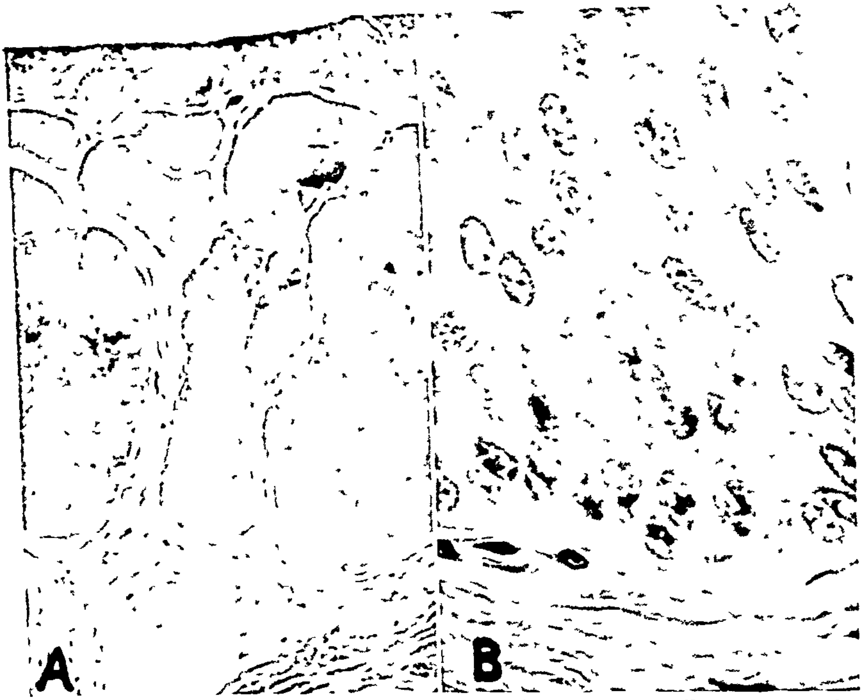

FIG 2 Case 1 *A*, low power photomicrograph showing no papillary outgrowth, but broad cords of well differentiated epithelial cells infiltrating submucosa and muscle. *B*, high power showing regular size and shape of well differentiated transitional type of epithelial cells

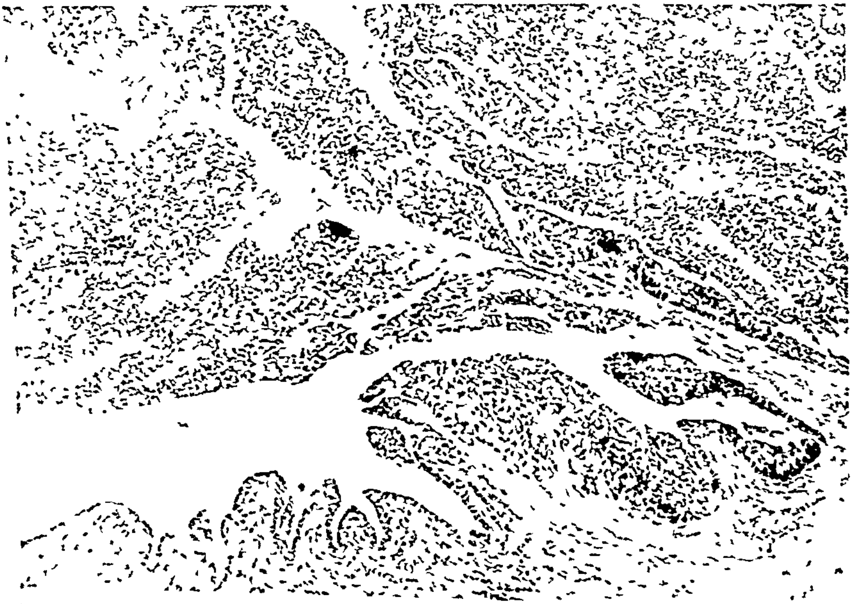

FIG. 3 Case 2 Low power photomicrograph showing normal epithelium at lower left and papillary outgrowth of tumor.

a history of hematuria and vaginal bleeding, for which a vaginal polyp had been removed 8 months before. Since then the hematuria had been intermittent. Cystoscopic examination in the office was unsatisfactory because of bleeding from the right ureter, and she was admitted to St. Luke's Hospital the following day.

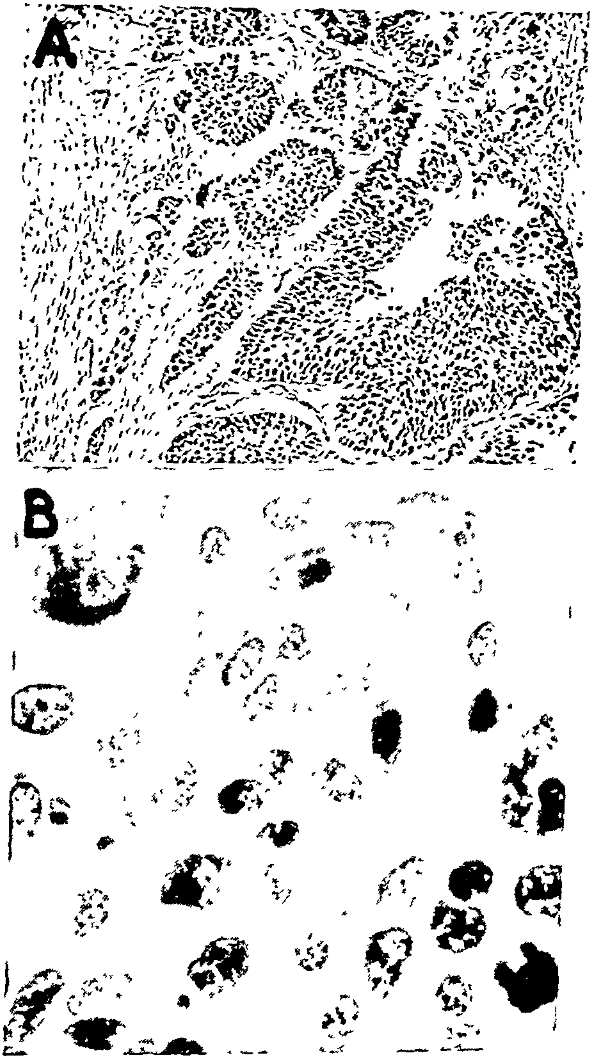

FIG. 4. Case 2. *A*, another area, low power, showing invasion or infiltration of muscle wall. Variation in size and shape of cells is evident. *B*, high power showing variation in size and shape of epithelial cells and mitotic figures.

General physical examination showed an obese, elderly woman, who looked anemic. She had a systolic apical murmur, with an accentuated aortic sound. Blood pressure was 180/100. On the basis of history and physical examination, a provisional diagnosis of carcinoma of the upper urinary tract and hypertensive cardiovascular disease was made. Her blood count on June 3, 1949 showed 9 gm. hemoglobin, 62 per cent and 2,900,000 red blood cells. After three transfusions of 500 cc blood, she had 12.5 gm. hemoglobin, 86 per cent, and 4,400,000 red blood cells. The blood chemistry was normal. The report on the x-ray of the chest read: "No pulmonary pathology noted."

On repeat cystoscopic examination, there was a clot protruding from the right ureteral orifice, and after this was removed, a papillary growth was seen filling the orifice. The left ureter was catheterized. The urine from the left kidney was normal, and phenolsulfonphthalein intravenously appeared in 3 minutes in good concentration from that side. A left ureteropyelogram was within normal limits.

On June 11, 1949, the kidney was removed through a curved iliolumbar incision, and the lower ureter was removed through a midline suprapubic incision. Because of the low position of the tumor, the bladder was opened, and incised down to and around the right ureteral orifice. A cuff of vesical mucosa 3 cm. in diameter was left attached to the ureter, and then was used to cover the end of the ureter. After the lower end of the ureter was freed from the bladder wall, the resection was carried out from above retroperitoneally.

The pathological report (Dr. B. Earl Clarke) was as follows:

"Specimen consists of two portions:

"A, wrapped separately and labelled right ureter. The external surface is dull, opaque, and has numerous attached fibrous shreds. Over 11 cm. of length at one end, the ureter is firm and irregular with yellow fatty deposits on its surface.

"On opening the lumen the ureter is dilated with smooth, gray mucosa for a distance of 7 cm. At this point there is a gray, soft, sessile mass arising from the mucosa and measuring 2 by 1.3 cm. to a height of 8 mm. Similar growths are seen in the shorter of the two pieces of ureter.

"B, right kidney weighing 75 gm. with attached peri- and nephritic fat. It measures 9 by 5 by 2 cm. . . . .No cortex or pyramids are recognizable. . . .

"Microscopic description (figs. 3 and 4): Sections of ureter through the tumor masses reveal an area of transitional epithelium infiltrated by lymphocytes, plasma cells, eosinophiles, and fibroblasts. This gives way to a papillary, then sessile projecting mass of transitional epithelium composed of irregular strands, cords and sheets of large polygonal cells showing many mitotic figures. These cells invade the musculature of the ureter and in a few areas appear to have reached the serosa. A similar process is seen in the mass sectioned through the distal end of the ureter and bladder wall. However, the bladder epithelium does not appear to be involved beyond the mass except by lymphocytes and plasma cells invading the submucosa and muscularis.

"Sections of the kidney reveal hyalinized thickening and obliteration of the most peripheral vessels and glomeruli as well as diffused, generalized infiltration of the kidney parenchyma by lymphocytes, plasma cells, eosinophiles, and fibroblasts. Many of the tubules are obliterated while others show dilatation and flattened epithelium. The glomeruli show fibrous thickening and infiltration by mononuclear leukocytes. The calyces show extensive areas of granulation tissue.

"Diagnosis: Carcinoma of right ureter (transitional cell); chronic pyelonephritis, right; hydronephrosis, right."

In both of these cases, in order to insure adequate resection of the lowermost portion of the ureter, a cystotomy was done and a good cuff of mucosa was excised transvesically. Bovie and Bors had previously used this method.[15]

SUMMARY

Two cases of primary carcinoma of the ureter are reported, one single and the other with multiple growths.

Cystotomy was done in both cases to insure adequate resection of a cuff of vesical mucosa.

2 E. 54th St., New York, N. Y.

[15] Bovie, C. F. and Bors, E.: J. Urol., 54: 434, 1945.

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THE PHYSIOLOGY OF MICTURITION

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Our investigations in the physiology of micturition by means of fluoroscopy have been continued, so that to date more than 300 observations have been made. These observations have confirmed our views previously expressed, and this paper will briefly summarize them and emphasize a few new points.

THE VOLUNTARY MECHANISM

Man utilizes a group of striated, somatically innervated skeletal muscles by means of which he voluntarily controls micturition. This group of muscles which we have termed the "voluntary mechanism," consists of the thoracic diaphragm, the muscles of the abdominal wall and of the levator ani with its two component parts, the pubococcygeus and the ileococcygeus. Deliberate micturition at any degree of bladder filling begins with a moderate increase in intra-abdominal pressure which is directed toward the bladder neck. It is not generally appreciated that man can direct intra-abdominal pressure either toward the bladder neck for purposes of micturition, or toward the anus for purposes of defecation. These are two separate and distinct maneuvers, brought about by a different application of the same muscle groups. The increase in intra-abdominal pressure at the beginning of micturition, caused by the action of the thoracic diaphragm and of the abdominal musculature, is associated with a relaxation of the pubococcygeus. This muscle is intimately connected with the bladder neck in the female, and is slung beneath the prostate in the male. The two maneuvers, i.e. the directed pressure toward the bladder neck, and the prompt relaxation of the pubococcygeus, cause the bladder neck to be pushed downwards in the pelvis, and it is this downward tug on the bladder neck which acts as the stimulus for the contraction of the detrusor (fig. 1). The bladder neck is thus the "trigger area," and it is at this point that the voluntary mechanism and the involuntary detrusor are joined. The impulse for the contraction of the detrusor spreads from the bladder neck to the base, the sides, and to the dome. In most individuals these steps occur very quickly and smoothly. Occasionally, however, one encounters a detrusor whose component parts go into action in a slow motion-like manner.

For normal micturition the voluntary increase in intra-abdominal pressure is not a severe straining effort,—far from it. Indeed, when it becomes a severe straining effort and an improperly directed force, it will fail altogether to precipitate the reflexes of micturition. One sees precisely such an effort in inhibited individuals who cannot void in the presence of others. They overdo in their attempt to void, and misdirect a rather severe straining effort downwards onto the entire pelvic floor so that the whole bladder base sags (fig. 2), and the

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Read at annual meeting, American Urological Association, Washington, D. C., May 29, 1950.

bladder neck itself is not stimulated to initiate the detrusor contraction. The effort must be directed in a circumscribed manner to the bladder neck to be effective.

This does not hold true for certain neurogenic dysfunctions associated with flaccid abdominal and pelvic muscles. In such patients, straining efforts, though not physiologic and not properly directed in the sense as they have been described above, will initiate micturition, but this type of micturition must not be confused with the events in the normal individual, for in neurogenic disease the behavior of the detrusor is abnormal as well.

Inability to raise intra-abdominal pressure, coupled with improper direction of whatever pressure is raised, will make deliberate initiation of the urinary stream difficult, if not impossible. This combination of factors is seen in patients who have had operations on the lower abdomen, pelvis or perineum. The fresh incision is associated with spasm of the musculature, especially so in sensitive individuals. It is common knowledge that coughing or straining is difficult under those circumstances. The inability to utilize the abdominal wall or the pelvic floor thus contributes significantly to the development of postoperative urinary retention. The perineal wound in patients who have had abdomino-perineal resection of the rectum for cancer would seem, for similar reasons, to preclude normal micturition.[1]

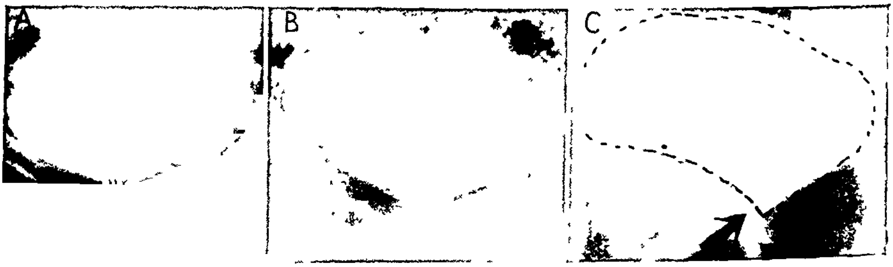

FIG. 1. *A*, bladder at rest. Note base line. *B*, bladder at beginning of micturition. Note precision with which bladder neck has been pushed down. *C*, same as *B*. Oblique view.

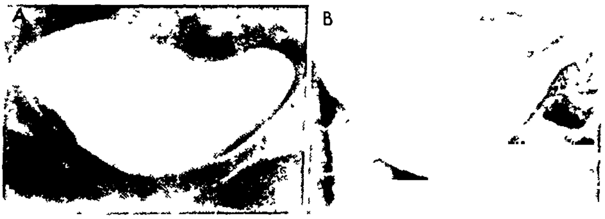

FIG. 2. Nullipara, normal control. Patient could not void in presence of bystanders. *A*, bladder at rest. Note base line. *B*, futile attempt at micturition. Note downward displacement of entire bladder base instead of bladder neck, as in figure 1, *B*.

A particularly fertile field for the study of the effects of the dysfunction of the levator ani on normal micturition is afforded in cases of multiple sclerosis. These patients have various degrees of flaccidity of the muscles of the pelvic floor, and can be shown to have a proportionate difficulty in starting or stopping the urinary stream. The pathologic physiology of micturition in multiple sclerosis is discussed more fully in another publication.[2]

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[1] Marshall, V. C., Pollack, R. S. and Miller, C.: Observations of urinary dysfunction after excision of the rectum. J. Urol., 55: 409–416, 1946.

THE FUNCTION OF THE DETRUSOR

Anatomically the bladder base is thicker than the dome. This is in accordance with the function of these two parts of the bladder. The impulse for contraction is received by the bladder base first. It is thus first to contract, and with the contraction of the sides of the bladder, forces the dome upwards at the beginning of micturition. The bladder base furnishes the main expulsive power of the bladder, and can hypertrophy to two or three times the thickness of the dome when the outflow of urine is obstructed. This can be readily demonstrated during suprapubic prostatectomy. The base of the bladder may be found to be up to 2 or 3 cm. thick, while the dome is only 4 to 8 mm. in thickness.

Normally, the dome assists in the micturition efforts of the bladder base in two ways: First, by contracting and thus directing the hydrostatic pressure toward the internal sphincter and second, by propagating the peristaltic contraction wave which has originated at the bladder neck at the beginning of micturition. A dome which has become overstretched as a result of obstruction or neurogenic disorder, balloons out during micturition very much like a diverticulum of the bladder does. The patient then voids into the dome of his bladder just as he voids into a diverticulum. A bladder dome which balloons out fails to direct intravesical pressure downwards and makes micturition inefficient.[3]

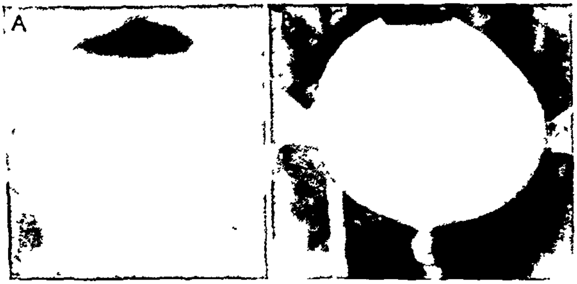

FIG. 3. *A*, child's bladder during micturition. Note spherical shape. *B*, young adult voiding. Note spherical shape of bladder.

In children and in many adults the contracting detrusor takes the shape of a sphere (fig. 3). From the point of view of physics, this is the most efficient form it could take in order to produce a maximum internal pressure with a minimum of effort on the part of its own wall.[4] There are exceptions to this, however. Not infrequently the bladder may retain an asymmetrical or even a triangular shape during micturition, and yet succeed in emptying its contents easily and completely (fig. 4). In obstructive and neurogenic lesions some portions of the bladder muscle become weaker or thinner. The weaker part yields to the increased intravesical pressure, and the bladder then assumes a lop-sided appearance. In children, the events during micturition occur with great promptness and smoothness. It has been shown that the infant's bladder is wholly automatic, i.e., it responds to the stretch reflex only, and empties spontaneously when the proper amount of urine has accumulated in the bladder to precipitate this reflex. Between the ages of 1½ and 2½ the child develops bladder sensations, and will signify the imminent desire to void. At this stage the child can as yet not inhibit the detrusor too well, nor can it void at will when the bladder contains less urine than is needed to produce the stretch reflex. Between the ages of 2½ and 4 the child learns to induce a detrusor contraction at will, although at first with considerable hesitation. It can now stop and start the urinary stream with ease. In the child, very little relaxation of the pubococcygeus is needed to induce a detrusor contraction. The reflexes are promptly executed, and in response to the contraction of the detrusor, the proximal urethra can be seen to open up widely.

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[2] Muellner, S. R., Loman, J. and Alexander, L.: The urinary bladder in multiple sclerosis. In press.

[3] Muellner, S. R.: The physiologic components of the urinary bladder. N. Eng. J. Med., 241: 769-772, 1949.

[4] Ashley, H., M.I.T. Personal communication to the author.

FIG. 4. Note irregular contour of bladder during micturition

A widely open proximal urethra in the adult occurs when the bladder has become unduly stimulated. The detrusor can then be seen to go into spasm, and to contract strongly in its entire circumference, much more so than for normal micturition. This is associated with a particularly wide opening of the proximal urethra, and suggests that man possesses vesico-urethral reflexes which in effect appear to be designed to rid the urinary passages of noxious substances. These reflexes are most readily demonstrated in some patients with multiple sclerosis who have hyperirritability of the detrusor and of the urethra (fig. 5).

THE VOLUNTARY INTERRUPTION OF THE URINARY STREAM

It has been assumed that man deliberately contracts the external sphincter when he wants to stop his urinary stream. The external sphincter, consisting of striated muscle, somatically innervated, it is said, could be closed yet not opened, at will. This assumption is not correct. There are no proprioceptive fibers leading to the external sphincter, and one cannot contract just the external sphincter any more than one can contract wilfully the internal oblique muscle alone. The deliberate interruption of the urinary stream is a much larger effort, and consists of the contraction of the entire levator ani. This sharply raises the bladder neck and causes the internal sphincter to snap shut. The urinary stream is therefore interrupted first at the internal sphincter, and one never sees the stream to be pinched off by the external sphincter when urination is deliberately stopped.

A normally functioning levator ani is thus necessary if the urinary stream is to be stopped at will. A levator ani which has lost much of its tonicity, although not paralyzed by destruction of its nerve supply, becomes an inefficient mechanism for the deliberate interruption of the urinary stream. One sees this in women who have severe urinary stress incontinence. The levators are quite relaxed, and when the urinary flow has been induced by the sudden stress they cannot stop the stream because of their inability to contract the levators with sufficient force to raise the bladder neck up. The etiology of this type of stress incontinence, as well as the kind seen in young girls and nulliparous women, has been more fully discussed elsewhere.[5] These findings have recently been corroborated by Marchetti.[6]

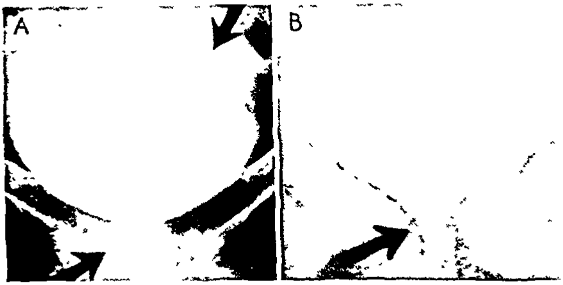

FIG. 5. *A*, bladder spasm. Note contracted detrusor (upper arrow) and widely dilated urethra (lower arrow). *B*, same bladder during normal micturition. Note that urethra is now much more narrow.

Inability to start or to stop the urinary stream at will is also seen in late stages of cancer of the prostate, when the infiltrative growth has fixed the gland in the pelvis so that the bladder neck can neither be raised nor lowered by the otherwise intact levators.

The above observations emphasize the importance of a normally innervated and functioning pelvic floor for normal micturition in man, and thus fail to substantiate the belief expressed by Langworthy[7] and his co-workers, that man voids by wilfully contracting his detrusor, a theory not in accord with the physiology of involuntary (smooth) muscle. The view proposed by Denny-Brown[8] that voluntary micturition is brought about by the removal of the inhibitory effect of the brain (will) on the detrusor, which then proceeds to contract, also could not be confirmed. Both theories fail to account for the function of the voluntary mechanism.

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[5] Muellner, S. R.: The etiology of stress incontinence. Surg. Gynec. & Obstet., 88: 237–242, 1949.

[6] Marchetti, A. A.: The female bladder and urethra before and after stress incontinence. Am. J. Obst. & Gynec., 58: 1145–1154, Dec. 1949.

[7] Langworthy, C. R., Kolb, L. C. and Lewis, L. G.: Physiology of Micturition. Baltimore: Williams & Wilkins, 1940.

[8] Denny-Brown, D. and Robertson, E. G.: On the physiology of micturition. Brain, 56: 149–190, 1933.

SUMMARY

Observations based on 300 bladder fluoroscopies confirm the importance of a properly functioning pelvic floor, abdominal wall and thoracic diaphragm for physiologic micturition in man. Dysfunction of these muscles, and especially those of the pelvic floor, is shown to have a direct bearing on man's ability to stop or to start his urinary stream at will. The function of the component parts of the detrusor is described, and the clinical significance of these findings is discussed.

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DISCUSSION

Dr. W. Joseph McMartin (Omaha, Neb.): We are indebted to Dr. Muellner for continuing his investigations of the physiological principles of micturition. This field of neurophysiology is a very controversial one. Differences of opinion exist between physiologists, anatomists and surgeons.

I agree that Dr. Muellner has demonstrated definitely that the pubococcygeus, iliococcygeus, the thoracic diaphragm and the muscles of the abdominal wall are great factors in the voluntary control of urination.

Several other muscles operate in a definite firing order with these muscles. The filling of the bladder is a parasympathetic reflex entirely, mediated through stretch reflexes in the mucosa and wall of the bladder which reach the cord by means of afferent fibres of S_2 and S_3. These impulses are sent back to the bladder over the same nerves from the cord without reaching any higher centers until cortical control of micturition has developed. When cortical control has developed all information regarding micturition is sent to the cortex in the normal individual. This initiates a series of changes, the first of which is somatic. The somatic change is first in the lowering of the bladder due to relaxation of the pubococcygeus muscle, and relaxation of the deep transversus perinei muscle, and this allows the stream of urine to pass through the urethra uninterrupted. When micturition is stopped whether the bladder is empty or not, and it is stopped under volitional control there is first a contraction of the bulbocavernosus muscle. When the bulbocavernosus contracts, there is simultaneously a contraction of the deep transversus perinei muscle which closes off the membranous portion of the urethra by pulling the urethra upward and forward. The urine within the bulb of the urethra is compressed out of the urethra by contraction of the bulbocavernosus. The urine cannot be compressed from the bulb back into the bladder because of the simultaneous contraction of the deep transversus perinei muscle with that of the bulbocavernosus muscle. The bladder is elevated and pulled forward by the bulbococcygeus.

The internal sphincter is part of the detrusor muscle and acts mechanically as a part of it. The volitional part of urination ends with relaxation of the pubococcygeus and the transversus perinei muscle and the start of the urinary stream. The emptying of the bladder is performed by the detrusor muscle. This is a reflex mechanism.

I ask that Dr. Muellner explain how impulses for contraction of the detrusor muscle spread from the bladder neck to the base, the sides and then to the dome of the bladder. There can be no nerve connection between the pubococcygeus muscle and the detrusor muscle because the pubococcygeus is innervated by somatic nerves from the fourth sacral and the detrusor by parasympathetic nerves from the second and third sacral nerves. I think this is a reflex mechanism. The initiation of the contraction of the detrusor is by the stretch reflex.

I disagree with Dr. Muellner in that he has disproved the belief expressed by Langworthy and his co-workers, that man voids wilfully by contracting his detrusor, or disproved the view proposed by Denny-Brown that voluntary micturition is brought about by the removal of the inhibitory effect of the brain on the detrusor, which then proceeds to contract. I think that the parasympathetic nerves to the detrusor carry fibers that are under limited control of the cortex due to the fact that with but a few cubic centimeters of urine in the bladder man can empty the bladder entirely at will even though he has very little stretch reflex to the detrusor. This means that the detrusor can be stimulated by the will. We know that the parasympathetic fibers in general are under a limited amount of cortical control. This can be seen in actions on the diaphragm, and in the reflex of respiration.

I hope that Dr. Muellner can develop a method to show the act of urination as viewed from the lateral aspect of the pelvis. In this way he might be able to show the changes in shape of the neck of the bladder anteroposteriorly as he has depicted so well transversely. The fluoroscope might also give us a better view of the succession in action of the pubococcygeus, the deep transversus perinei and the bulbocavernosus muscles.

DR. S. RICHARD MUELLNER (Boston, Mass.): I want to thank Dr. McMartin for his kind remarks and his able discussion.

I have time to elaborate on one point, and that is, that I did not mean to imply that the innervation of the pubococcygeus and the ileococcygeus are necessarily the same as that of the detrusor, or that nerve impulses from these muscles spread directly to the bladder. Man, however, does utilize these striated, voluntary muscles with which to motivate his detrusor. The mechanism is thus not a direct but an indirect one.

The voluntary initiation of the urinary stream is therefore as follows: As a result of the increase in intra-abdominal pressure, brought about by the contraction of the thoracic diaphragm and the abdominal musculature and the concomitant relaxation of the pubococcygeus, the bladder neck is pushed downwards. It is this downward push on the bladder neck, or the region of the internal sphincter, if you will, which sets off the reflexes of the detrusor itself. The "trigger area" is thus the region of the bladder neck. It is this area which first receives the stimulus for the contraction and for the relaxation of the detrusor, respectively. From this point the impulse for the contraction of the detrusor spreads to the sides and then to the dome of the bladder. All this occurs quite quickly.

In the course of the many fluoroscopic studies of the bladder which we have done, to date, one finds some individuals who are perfectly normal but in whom the detrusor reacts in a leisurely fashion, so that the progressive contraction of the detrusor from the bladder neck to the sides and eventually to the dome of the bladder, can be very clearly observed.

Dr. McMartin asked if I had observed the side view of the bladder in action. We do this routinely, but we have ceased to make spot films of these views, since they are apt to be too thin or too dense for reproduction for slides or for illustrations. It is difficult for one who has never seen the bladder under the fluoroscope to appreciate, from a mere description of the process, exactly what goes on. Bladder fluoroscopy is really quite simple, and I suggest that you do it yourself on normal individuals, beginning perhaps with a study of a nulliparous female bladder, to appreciate fully the physiologic process of micturition.

To stop the urinary stream at will in the midst of micturition, man contracts the entire levator ani muscle. If you observe very carefully what you do yourself when you deliberately inhibit the urinary stream, you will become aware of the use you make of your levator ani. The contraction of the levator ani raises the bladder neck and permits the internal sphincter to snap shut. During micturition the intravesical pressure is concentrated and directed toward the bladder neck. When the bladder neck is raised, the pressure against it seems to cease, and one can then see the detrusor gradually relax to its resting phase. I have never seen the stream interrupted by the action of the external sphincter alone.

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EXPERIMENTAL VESICOSIGMOIDOSTOMY

W. L. CHAMPION, M. F. FOWLER, R. C. COLEMAN, JR. AND T. J. FLORENCE

This is a report on an animal experiment which consisted of the artificial anastomosis of the urinary bladder to the lower bowel with concomitant occlusion of the urethra.

A female dog, 2 years of age, weighing 12 kg., was selected. Excretory urograms were performed before and after surgery. Because of technical difficulties in reproducing the x-rays as pictures, they do not appear in this article. However the actual films were mailed to the editors for their examination. On the preoperative roentgenograms the kidney pelves and ureters were visualized. Both sides were normal. The bladder could be seen as a large abdominal organ.

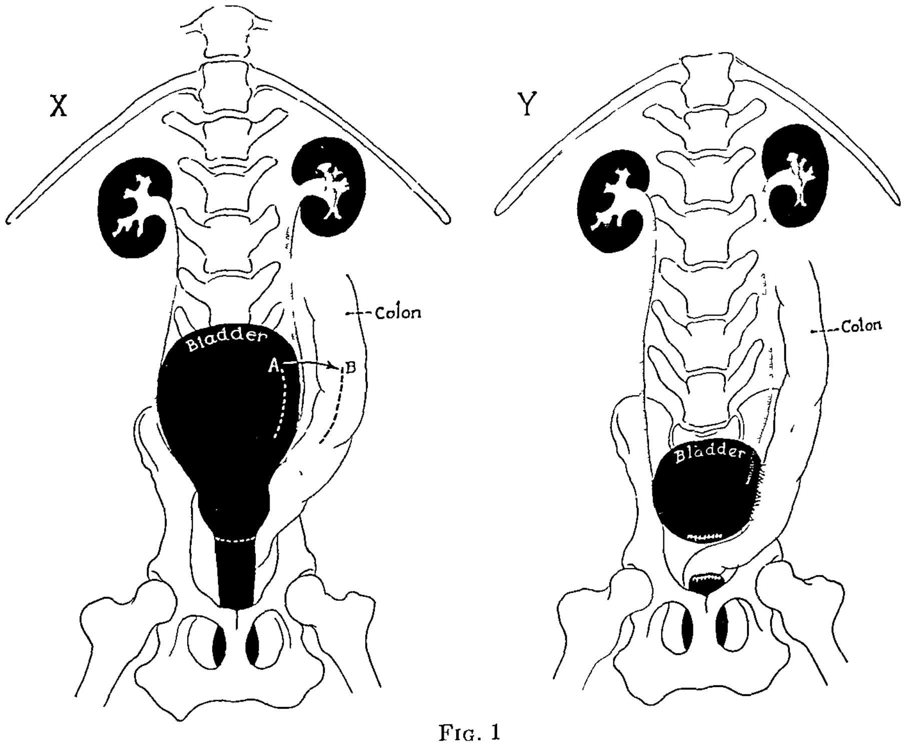

FIG. 1

The animal was placed on a low residue diet. No enemas, laxatives, or antibiotics were given. On June 16, 1950, under intravenous "one shot" nembutal anesthesia, a vesico-colic anastomosis with partial resection of the urethra and bilateral occlusion of the fallopian tubes was performed. This is shown in figure 1. The abdominal cavity was opened by a midline incision from the symphysis pubis to 3 cm. above the umbilicus. As could be seen by the x-rays, the bladder was an abdominal organ with the urethra being fully 5 cm. in length. The urethra was doubly clamped near the bladder, severed, and both ends securely closed with No. 1 chromic catgut. Then without distorsion or tension the left side of the bladder and the lower sigmoid colon were placed in apposition. A running suture of atraumatic "00" chromic catgut was used to approximate the serosal surfaces of the two organs for a distance of 3 cm., leaving a free end of suture at each end of the closure. Then the entire bladder wall was incised for an equal distance about 2 mm. above the suture line. A like incision was made in the opposite bowel. A separate atraumatic suture of "00" chromic catgut was used to anastomose the mucosa of the bladder and intestine completely around the artificial opening. The free ends of the original serosal suture were then used to complete the lateral and anterior approximation of intestine and bladder wall. Upon completion there was an orifice between the bladder and bowel with a large diameter of 3 cm. and the walls of the two organs were held together by two layers of continuous sutures. The ureters entered posteriorly to the anastomosis and were not disturbed. The abdominal incision was closed with interrupted sutures of "00" chromic catgut.

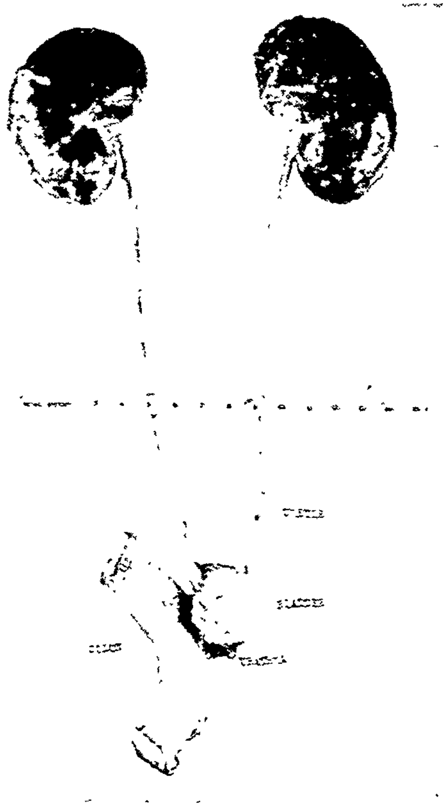

FIG. 2

Following surgery 300,000 units of penicillin were administered intramuscularly. The wound healed per primam. The dog drank water the next day and

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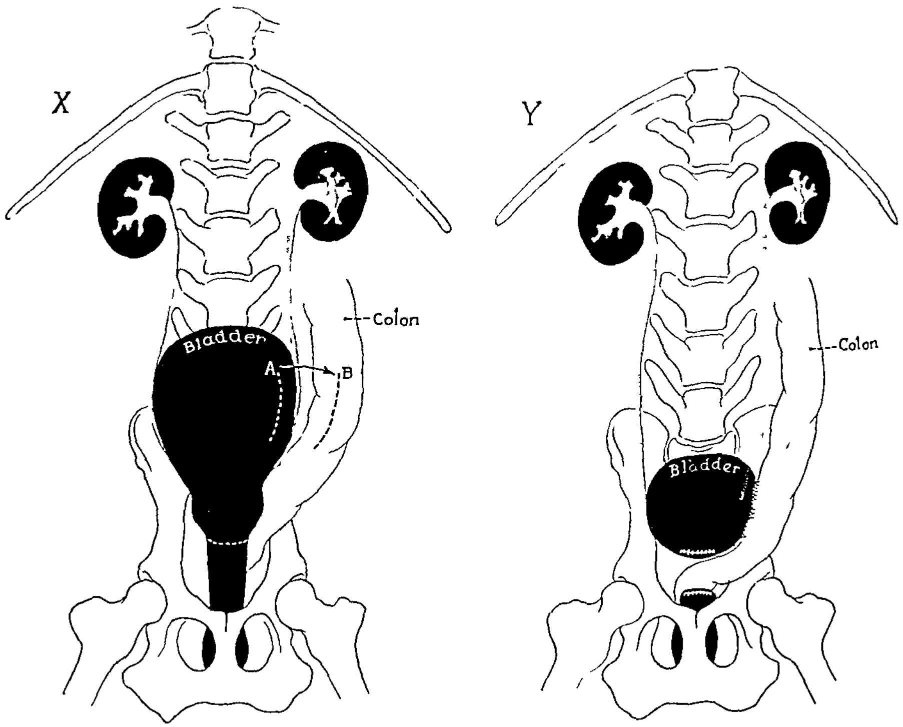

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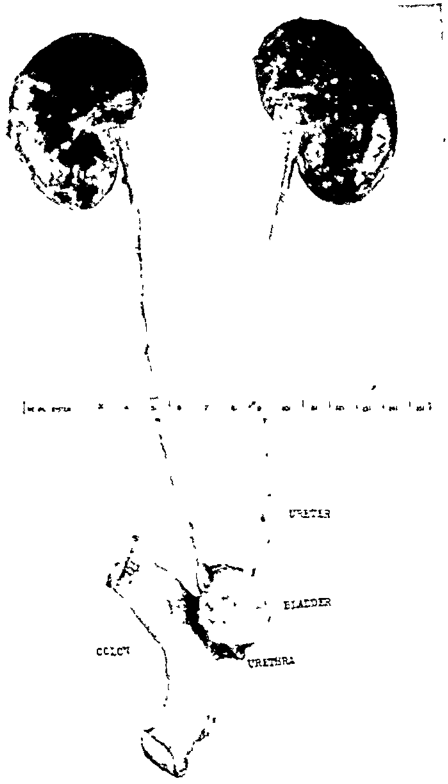

Fig. 2

Following surgery 300,000 units of penicillin were administered intramuscularly. The wound healed per primam. The dog drank water the next day and was active about the area of confinement. No evidences of peritonitis or urinary sepsis such as abdominal distention, abdominal rigidity or hyperpyrexia were seen. The general health of the animal stayed about normal. However there was a progressive loss in weight which might have been due to developing uremia from intestinal absorption of the nitrogenous products in the urine as has been shown to be true for the dog. There were from 6 to 12 stools each day which were liquid with suspended solid material.

Excretory urograms were repeated on July 27, 1950, or 6 weeks after surgery. These revealed no ureteral or pelvic dilatation. The bladder could not be seen but an ovoid mass of the contrast medium was present in the mid-pelvis, presumably in the colon.

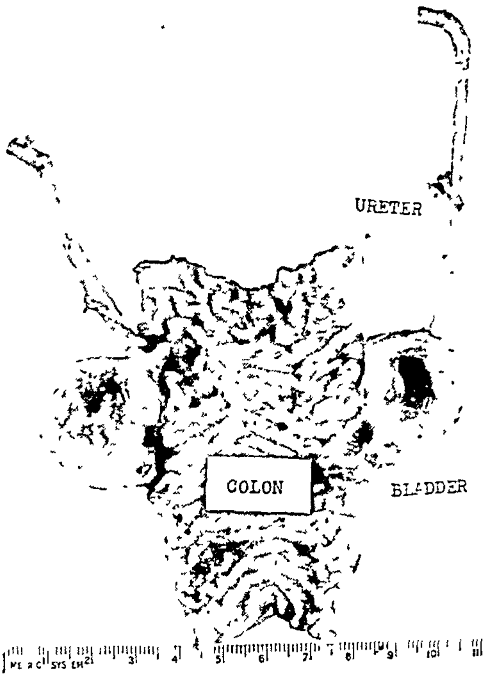

FIG. 3

On August 11, 1950 the dog was given a lethal dose of intravenous nembutal. An autopsy was then performed. The area of anastomosis was well healed with no adhesions. As can be seen in the photographs (figs. 2 and 3) there was no obstructive dilatation of the ureters or pelves. The bladder had contracted down so that it appeared in relation to the colon as a knot on a tree. Then the area of anastomosis was opened. The lumen had preserved its wide caliber and the mucosal surfaces of the bladder and bowel seemed to be faring well under the impact of their unusual contents.

COMMENT

There are occasions when the diversion of urine to the large bowel seems to be indicated. To our knowledge, this either has been done by the popular method of ureterosigmoidostomy or the old unsuccessful method of placing the trigone in the intestine. It appeared to us that at times the bladder might be preserved in all or in part, as, for example, in urethral injury with incontinence or in severe urethral stricture. Therefore, if surgically and physiologically feasible, a lateral anastomosis of the bladder and the lower bowel would be technically more simple and would insure against lower ureteral obstruction. The animal experiment reported here seems to support this view.

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CONSIDERATION OF PROBLEMS INCIDENT TO PERFORMANCE OF URETERO-ENTEROSTOMY: REPORT OF A TECHNIQUE

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The following comments on the technical performance of uretero-enterostomy are suggested by the writer's experiences, good and bad, in performing this operation. They are offered at this time to bring up once again a discussion of basic principles. This seems warranted inasmuch as the variety of published techniques, all purported to give good results, leave the average urologist wondering which operation may be expected to give the best results, and consequently the one that should be mastered. Unfortunately, the limited number of cases available for operation to any but surgeons in large hospitals and clinics make it virtually impossible to personally test varying techniques on enough cases to allow the operator to be sure which technical factors are responsible for good and poor results.

In view of the reports of Nesbit[1] and Cordonnier[2] advocating some type of direct bowel-ureteral anastomosis, and those of Huggins,[3] Brunschwig,[4] Kerr and Colby[5] advocating simple stab wound implantations of the ureter into the bowel, one wonders whether there is any advantage in performing a more difficult operation utilizing the Coffey principle of formation of a submucous tunnel. Many times I have heard surgeons say 'the simplest technique is the best.' I wonder whether this is true. There seems to be no doubt that good results have been obtained by the use of any method now generally utilized and perhaps no one method fits all cases ideally.

The only way to settle this matter, so far as I can see, is for relatively disinterested surgeons to pass on results obtained by different techniques after a considerable period of observation in an effort to analyze the factors which have led to poor results or those which have given good results. This has never been done to my knowledge and would make an interesting study.

However, it is difficult, even for the operating surgeon, to evaluate his own results accurately because so many factors are involved other than the 'method' utilized in joining the ureter and bowel. Thickness of bowel, redundancy or lack of it, preparation of the bowel, soiling of the operative field, redundancy of the ureter, size and thickness of the ureter, alignment of the ureter, relation of peritoneal edges to ureter in close proximity to the bowel—all may have as much to do with the ultimate result as the 'method' itself.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

[1] Nesbit, R. M.: Ureterosigmoid anastomosis by direct elliptical connection: A preliminary report. J. Urol., 61: 728–734, 1949.

[2] Cordonnier, J. J.: Ureterosigmoid anastomosis. J. Urol., 63: 276–285, 1950.

[3] Huggins, C. and Johnson, M. A.: Cancer of bladder and prostate. J. A. M. A., 135: 1146–1152, 1947.

[4] Brunschwig, A.: Complete excision of pelvic viscera for advanced carcinoma. Cancer, 1: 177–183, 1948.

[5] Kerr, W. S. and Colby, F. H.: Pelvic lymphadenectomy and total cystectomy in treatment of carcinoma of bladder. Trans. Am. Assoc. Genito-Urin. Surg., 41: 57–66, 1949.

In my own experience, utilizing the Coffey I technique, it has been apparent, from autopsy studies of the few patients who have thus far died, that there have been three principal causes for ureteral obstruction and consequent dilatation of the upper urinary tract when it existed. (No patient died from urinary tract disease or showed signs of active renal infection.) These factors have been 1) stricture of the tip of the ureter at the point where it made contact with the bowel lumen; 2) stenosis of the ureter due to peri-ureteral scar in the course of its passage through the bowel wall; 3) obstruction due to angulation or fibrosis about the lower ureter just above the site of entry into the tunnel in the bowel wall.

I have felt that strictures of the terminal ureter are more or less inevitable when any 'implantation' technique is used, inasmuch as healing of the ureteral tip occurs in the presence of infection and slough, and contraction necessarily often results. This problem would seem to be effectively eliminated only by utilization of a 'direct anastomosis' technique.

Stenosis of the ureter in its course through the bowel wall is undoubtedly a hazard of any 'tunnel' technique and may be due to organizing hematoma, infection or reaction by contamination from the bowel lumen, or leakage of urine or bowel contents from the bowel into the tunnel about the ureter perhaps due to retraction of the ureter or too large an opening in the bowel mucosa. These troubles would seem best prevented by careful hemostasis and the use of the 'direct anastomosis' technique which forms an almost water-tight anastomosis.

Stricture may also result from a tight implantation. Improper formation of the tunnel in the bowel wall due to failure to carry the incision deep enough toward the bowel mucosal layer and to dissect the mucosa from the overlying muscle layers far enough laterally on either side is, I believe, the chief cause. If this is not done properly, the ureter is made to lie between a relatively nonyielding submucosa and resutured muscle layers. When it is performed properly, the mucosa acts as a hammock which invaginates into the bowel and a 'tight' anastomosis does not result. Schnittman's paper[6] has been of great help to me in this regard, since I am sure that formerly my bowel dissection was inadequate.

Obstruction due to troubles above the anastomosis itself can be prevented by, first, careful measurement of the ureter before anastomosis so that no redundancy results; in addition by proper alignment of the bowel, anastomosis and ureter as the latter emerges from the retroperitoneum.

It has seemed to me that there are arguments pro and con which must be considered in relation to the direct anastomosis technique. For instance, if one is to implant dilated ureters by either Nesbit's or Cordonnier's method, I believe there is considerable chance that gas or fecal material may pass from the bowel into the ureter. I doubt that this occurs when the tunnel principle is used. In fact we have never demonstrated any reflux from the bowel into the ureter by barium enema when thin barium mixtures have been used. Perhaps a valve as such is not formed, but in any case this type of uretero-enterostomy appears to function in much this way. In implanting or anastomosing normal ureters, so long as the lower ureter at the site of implantation is not obstructed, it would

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[6] Schnittman, M.: Results in uretero-intestinal anastomosis. J. Urol., [illegible]

seem that a tunnel is unnecessary, though on the other hand it would do no harm provided a stricture did not result. I believe there is intrinsic value in the use of the Coffey principle and that technical improvement in this type of ureteroenterostomy may lead to a more satisfactory method of performing this most intriguing operation. With these thoughts in mind, I decided to perform ureteroenterostomy by making a direct anastomosis between the mucosa of the bowel and the full thickness of the ureteral wall, at the same time constructing a trough or tunnel to enclose the distal ureteral segment—a combination of the direct anastomosis and tunnel principles.

We have performed the operation on 8 cases and will discuss it under the following headings: 1) preoperative preparation of the patient; 2) abdominal exploration; freeing of the sigmoid; choice of sites for anastomoses; 3) identification, division, and preparation of the ureters; 4) preparation of bowel for anastomosis; 5) performance of the anastomosis; immobilization of the bowel; 6) postoperative care of the patient; 7) results.

PREOPERATIVE PREPARATION OF PATIENT

This requires 4 days and begins with catharsis using castor oil. A low residue, high protein diet is given. Enemas are used once each day with care to have the patient completely empty the bowel. On the morning of operation an enema is given and the lower bowel subsequently thoroughly washed out in the operating room with warm saline through a soft rectal tube. So far as antibiotics are concerned, to render the large bowel bacterial count as low as possible, we first used streptomycin, 0.5 gm. 4 times a day by mouth. More recently, since the report of Dearing and Heilman[7] from the Mayo Clinic, we have used 500 mg. aureomycin 4 times a day by mouth. Vitamins and blood are used as indicated. The evening before operation a Miller-Abbott tube is passed into the stomach. If it goes through into the duodenum, well and good; but if it does not, we are content to leave the tip in the stomach because, in the absence of real intestinal obstruction, we have found this provides for gastric and small bowel drainage quite as satisfactorily as a tube in the jejunum, and in addition eliminates the possibility of a collection of fluid in the stomach above the tip of the tube which sometimes leads to vomiting in spite of the presence of the tube in the jejunum. Spinal anesthesia has been used as the basic anesthesia supplemented as deemed necessary by the anesthetist.

OPERATION; EXPLORATION, FREEING OF SIGMOID IF NECESSARY, CHOICE OF SITES FOR URETERO-INTESTINAL ANASTOMOSES

For this we prefer a long, midline incision from the pubis nearly to the xiphoid. When the operation is to be done for cancer, after palpation of the liver, kidneys, retroperitoneal glands, and bladder, the small bowel is packed off and the sigmoid inspected and freed from the point where it leaves the left gutter to below the pelvic brim, thus giving as much mobility to this portion of the bowel as possible. The site chosen for anastomosis between the left ureter and bowel is just at the beginning of the sigmoid at the point where the bowel leaves the left gutter. Anastomosis is performed through an incision in the taenia on the anterior surface of the bowel as close to the mesenteric border as possible. We have found that the more natural course for the ureter from the retroperitoneum is through the mesentery of the upper sigmoid. When the anastomosis is done on the posterior surface of the sigmoid, it is difficult to be sure just how the ureter and the bowel adjust themselves when the bowel is replaced after the anastomosis, the chief difficulty, I think, being the question of redundancy or angulation of the ureter. The site for anastomosis of the right ureter to the bowel is determined by allowing the sigmoid to curve gradually across the midline without any redundancy to a point where it lies over the right ureter. We deliberately choose high sites in the bowel and well above the pelvic brim for two reasons. We think this results in redundant bowel below the anastomosis which serves as a urine reservoir and leads to better storage capacity and consequently less bowel frequency. We prefer to leave the pelvic portion of the ureters undisturbed in cancer cases and remove them together with all peri-ureteral tissues and common iliac glands along with the bladder. Postmortem examination of two cases of bladder cancer after uretero-enterostomy and cystectomy showed recurrent cancer at the sites of uretero-intestinal anastomosis, presumably because of involvement of lymphatics of the ureter. The approximate sites in the bowel

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[7] Dearing, W. H. and Heilman, F. R.: Effect of aureomycin on bacterial flora of intestinal tract of man. A contribution to preoperative preparation. Proc. Staff Meet. Mayo Clinic, 25: 87–102, 1950.

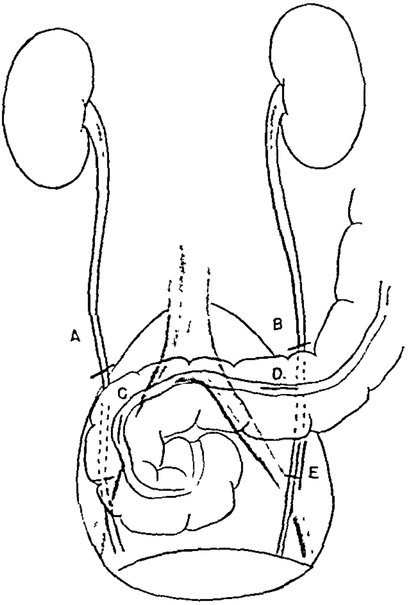

FIG. 1. Schematic drawing showing sigmoid bowel and upper urinary tract in relation to aorta and common iliac vessels. Sites for projected implantation of ureters into bowel are indicated at *C* and *D*. Sites of incisions in retroperitoneum for identification and division of ureters are indicated at *A* and *E*. Incision in mesentery of sigmoid through which left ureter is to be brought is indicated at *B*.

chosen for uretero-enterostomy, as well as incisions in the posterior peritoneum for division of the ureters, are shown in figure 1.

ISOLATION, DIVISION AND PREPARATION OF THE URETERS

The left ureter is exposed through a small incision in the retroperitoneum below the proximal sigmoid just above the pelvic brim. It is divided just above one clamp placed at this point. We believe that circulation in the proximal ureter may be arrested for a considerable distance proximal to a clamp which is allowed to remain on the ureter after its division. Resulting ischemia of the distal portion of the ureter may impair healing. The proximal cut end of the ureter is allowed to drain freely and bleed freely. The distal stump is tied and pushed down into the pelvis. The proximal ureter is freed very gently from its bed superiorly to a point behind the mesenteric border of the sigmoid through which an incision is made and through which the ureter is gently pulled. Under these conditions the blood supply of the ureter is provided by the lumbar arterial branch which enters the proximal ureter a relatively short distance above its severed end, much closer than if one were to utilize the pelvic portion of the ureter for anastomosis which, in our experience, almost always means dividing the arterial branch from the common iliac. Use of the lumbar ureter means, therefore, better blood supply of that portion of the ureter used for anastomosis. The ureter is measured accurately in relation to the point of anastomosis chosen on the sigmoid so that no redundancy or tension is likely after the anastamosis

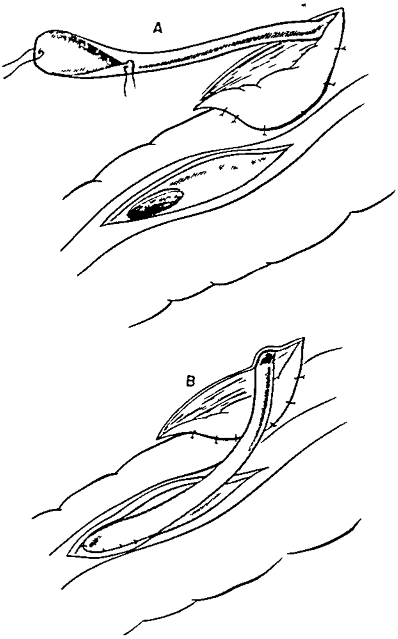

FIG. 2. *A*, suturing of mesenteric peritoneum to bowel wall close to site of trough which has been prepared in taenia. Also shown is ureter prepared for anastomosis. *B* demonstrates completed anastomosis between full thickness of ureteral wall and bowel mucosa.

has been performed. Usually a short segment is sacrificed. The end of the ureter is prepared for anastomosis by incising it for about 8 millimeters on the under surface and trimming off the sharp, square, distal points to provide an elliptical anastomosis as described by Nesbit. (See fig. 2, *A*.)

PREPARATION OF BOWEL FOR ANASTOMOSIS

A short segment of bowel in relation to the incision in the mesentery is chosen and a row of three or four fine silk sutures placed to approximate the inferior cut margin of the mesenteric peritoneum directly to the mesenteric border of the bowel. (See fig. 2, *A*.) The purpose of this is to lead the ureter directly to the site of anastomosis in the bowel without leaving any sharp peritoneal edge between the point where the ureter emerges from the loose connective tissue of the retroperitoneum and the point where it enters the bowel wall. An incision 2.5 cm. in length is made slightly diagonally across the anterior taenia from the mesenteric margin of the bowel. A trough is created in the bowel wall by incising the various layers down to the mucosa itself and gently stripping the mucosa away from the overlying muscularis thus forming generous flaps on either side, as described by Schnittman.[6] This is accomplished by incising the layers of the bowel wall very carefully at the distal end of the trough until the mucosa is identified, sometimes by actually perforating it. Having done this one can then dissect back along the incision within the proper layer. This, we think, is very important. It allows the mucosa to invaginate into the bowel lumen easily and after the ureter is placed in the trough the muscular flaps may be sutured over the ureter without compressing it in the least. The incision is carried back to the mesenteric margin of the bowel so that the ureter is subsequently led directly into this trough. The formation of the trough, in my experience, is often inadequately performed in that dissection is rarely carried deep enough toward the mucosa and the flaps of muscularis are not dissected laterally far enough on either side. Actually the dissection of the muscularis is best accomplished by stripping away the mucosa rather than stripping up the muscular layers, because if one gets into the proper plane of cleavage the mucosa seems to push away quite easily from the muscularis without much bleeding or trauma.

THE ANASTOMOSIS

A short opening is made through the mucosa at the distal end of the trough if it has not already been produced, and then a direct anastomosis performed between the prepared end of the ureter and the mucosa of the bowel, using interrupted sutures of fine arterial silk. This is accomplished by first placing two key sutures (fig. 2), one through the proximal end of the slit in the ureter, and one through the tip of the ureter. These are passed through the mucosa of the bowel proximally and distally, so far as the incision in the bowel mucosa is concerned, and tied. The intervening margins of ureter and mucosa of bowel are then sutured together using an additional four or five fine silk sutures on either side. The mucosa of the bowel is so delicate that it can be made to conform to the length of ureteral opening between the two key sutures without great diffichosen for uretero-enterostomy, as well as incisions in the posterior peritoneum for division of the ureters, are shown in figure 1.

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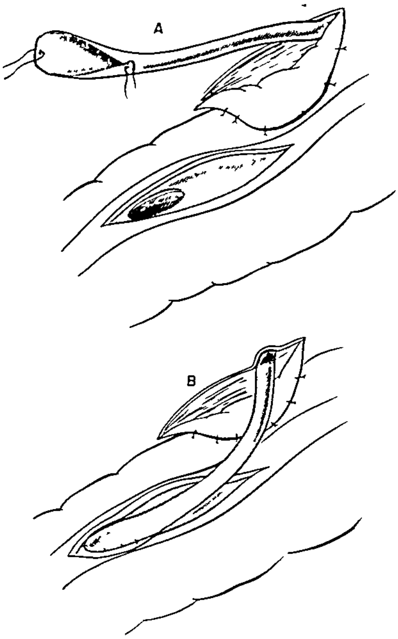

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edge of the mesenteric peritoneum over the site of anastomosis with very fine silk sutures. (See fig. 3, *A* and *B*.)

The right ureter is implanted utilizing the same technique, the ureter being approached through the posterior peritoneum directly at the point where anastomosis is to be done, well above the pelvic brim. It is freed only for a short distance, divided, and the bowel wall sutured to the margin of peritoneum below the point at which the ureter emerges. Anastomosis is then done in exactly the same way as on the left side and the bowel is immobilized by bringing the lateral flap of peritoneum over the area of anastomosis in the bowel just as on the left side. Additional sutures are placed to attach the sigmoid between anastomotic sites to the posterior peritoneum so that no small bowel hernia may develop between the sigmoid and posterior peritoneum.

POSTOPERATIVE CARE OF THE PATIENT

This has proved surprisingly simple. A long, soft rectal tube with multiple perforations is left in the rectum and held in place by adhesive strapping. It is connected to gravity drainage and irrigated with normal saline every 2 hours to keep the lumen free from fecal material. Usually urine is draining from the tube by the time the patient returns from the operating room. The Miller-Abbott tube is connected to gentle suction. Crysticillin and streptomycin are given intramuscularly for a few days until aureomycin can be taken by mouth. Intravenous fluids and blood are administered as indicated in terms of blood loss, urine output, and hydration. Complete blood chemistries are obtained daily for the first few days or until it is certain that renal function is satisfactory. Gastric suction is discontinued as soon as peristalsis is established, usually on the second or third postoperative day. Fluids and diet are started by mouth as soon as the patient tolerates them. The rectal tube is removed on the fifth or sixth day. Patients are instructed from the start to hold urine as long as possible inasmuch as habit frequency may otherwise develop and be difficult to modify. Excretory urograms are obtained within 2 weeks after operation.

RESULTS

During this past year ureterosigmoidostomy has been performed utilizing this technique on 8 patients. Bilateral operation was done in all but 1 case. The opposite ureter was ligated in this instance because the kidney had been blocked for some time and was nonfunctioning by excretory urogram. Indications for operation were interstitial cystitis in 1 case, cancer of the bladder or prostate in 7. Subsequent or simultaneous prostatovesiculocystectomy with regional pelvic gland dissection was done in 6 cases. One patient died 1 week after operation from pulmonary emboli. The postoperative period and subsequent course of the surviving 7 patients have been completely free from episodes of pyelonephritis. The most impressive, immediate result has been the free drainage of urine from the rectum from the time of operation and the absence of symptoms relative to the upper urinary tract. No evidence of leakage at the site of anastomosis has been noted and the lack of febrile reaction has been striking. One patient

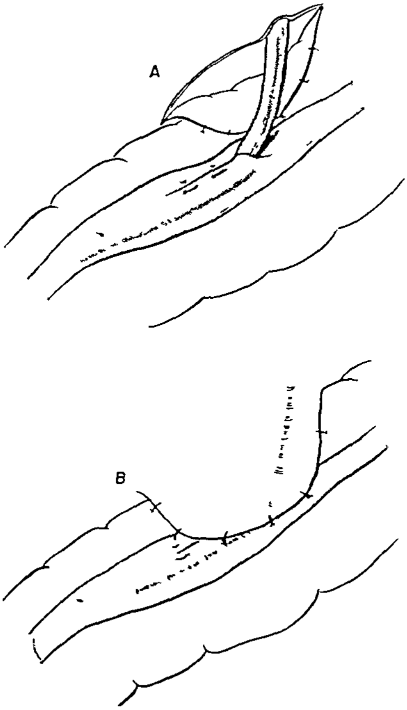


Fig 3. *A*, completed uretero-enterostomy; showing 2 sutures used to close margins of incision in bowel wall over ureter. *B*, superior margin of mesenteric peritoneum shown pulled down and sutured to bowel wall to extraperitonealize areas of anastomosis.

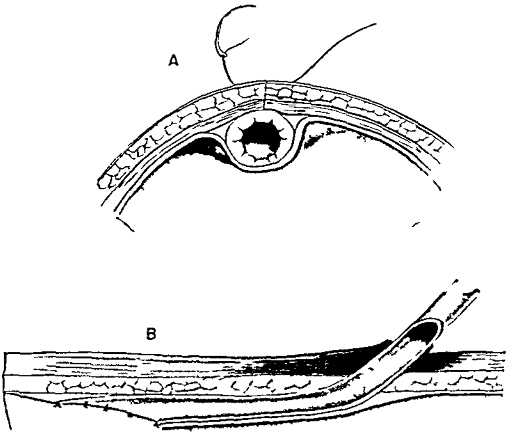


Fig. 4. Cross and longitudinal sections through bowel at site of uretero-enterostomy indicate author's concept of anatomical relationship after uretero-enterostomy has been properly performed.

culty, and practically a water-tight anastomosis is produced. No further fixation of the ureter is done, but the muscular flaps of bowel wall are then sutured loosely over the ureter using two or three fine silk sutures. Retroperitonealization of the anastomosis and fixation of the bowel are accomplished by suturing the superior

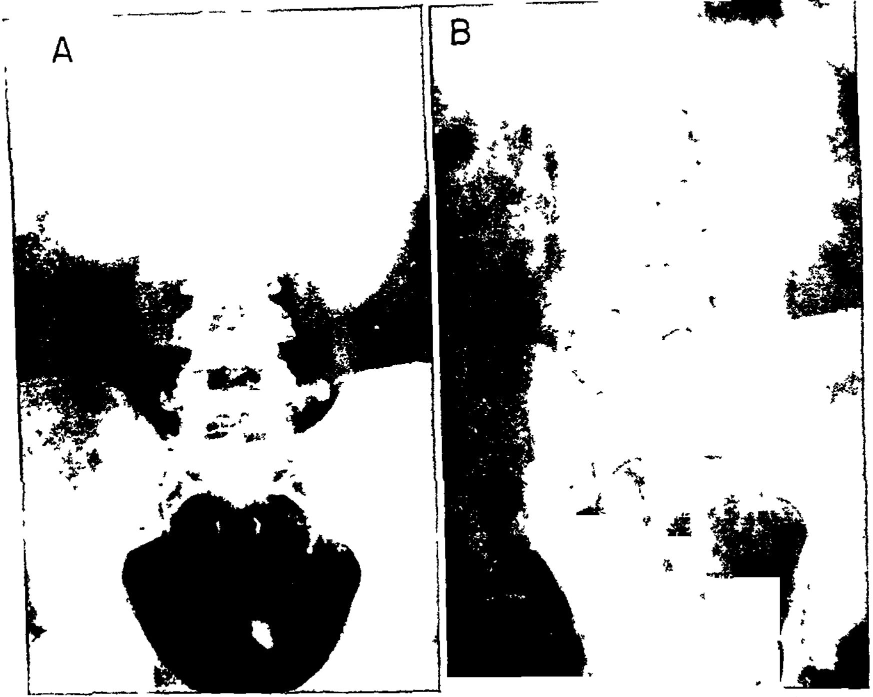


FIG. 7. Case 3. Man aged 61 with locally extensive carcinoma of prostate (triangular ligament involved). No apparent response to estrogen therapy. Bilateral uretero-enterostomy and radical prostatocystectomy with excision of triangular ligament. *A*, preoperative; *B*, postoperative urogram.

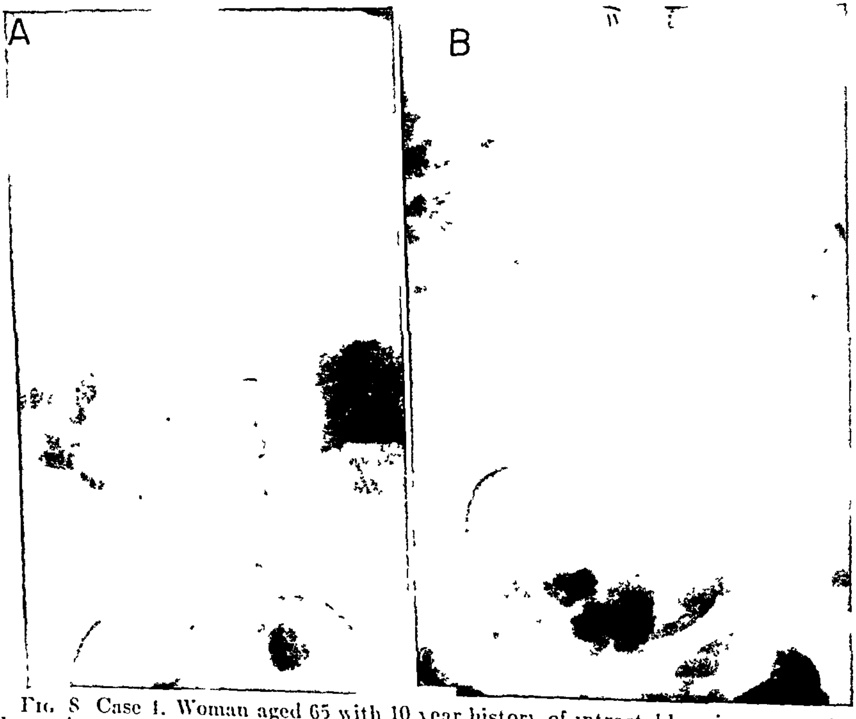


FIG. 8. Case 4. Woman aged 65 with 10 year history of intractable urinary complaints due to interstitial cystitis. Bilateral uretero-enterostomy with complete relief. *A*, preoperative; *B*, postoperative urogram. This was the poorest result.

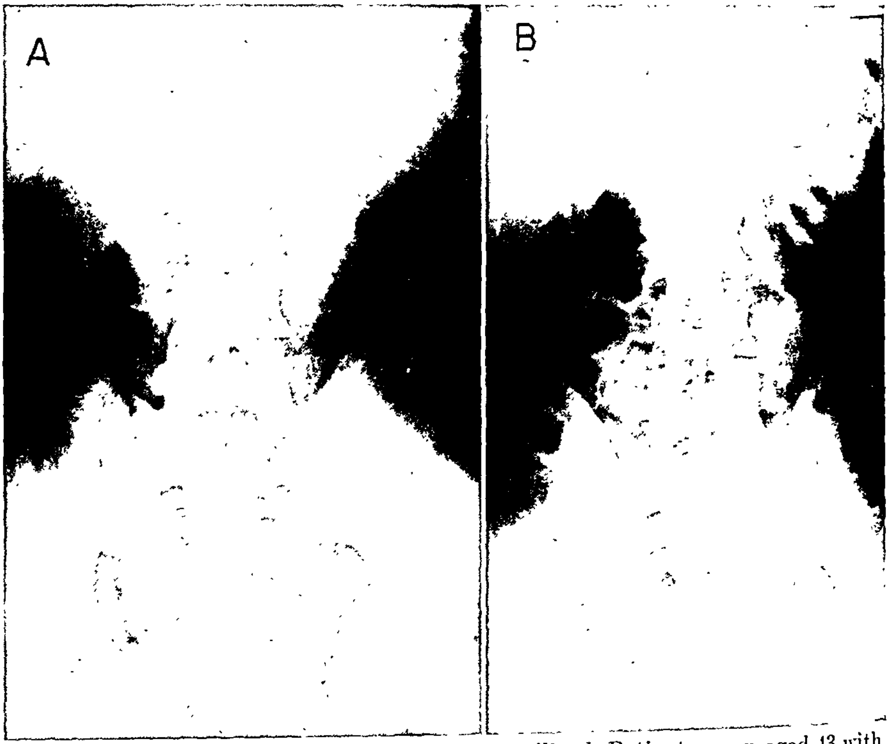


FIG. 5. First case in which this technique was utilized. Patient a man aged 43 with extensive carcinoma of prostate. Right kidney nonfunctioning. No response to orchiectomy Palliative left uretero-enterostomy. *A*, preoperative; *B*, postoperative urograms.

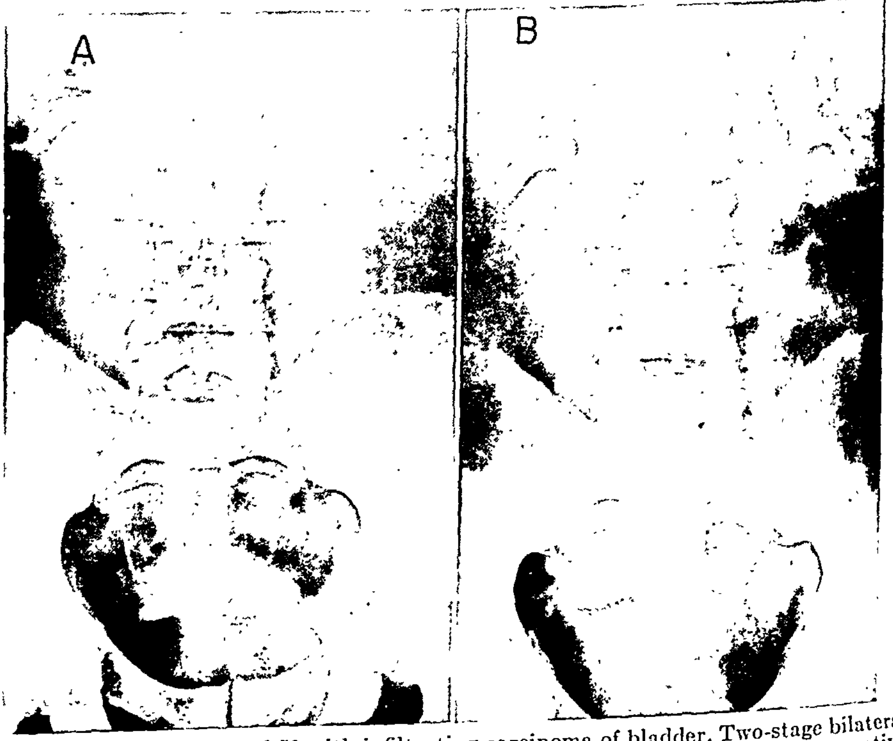


FIG. 6. Case 2. Man aged 50 with infiltrating carcinoma of bladder. Two-stage bilateral uretero-enterostomy and radical prostatocystectomy. *A*, preoperative; *B*, postoperative

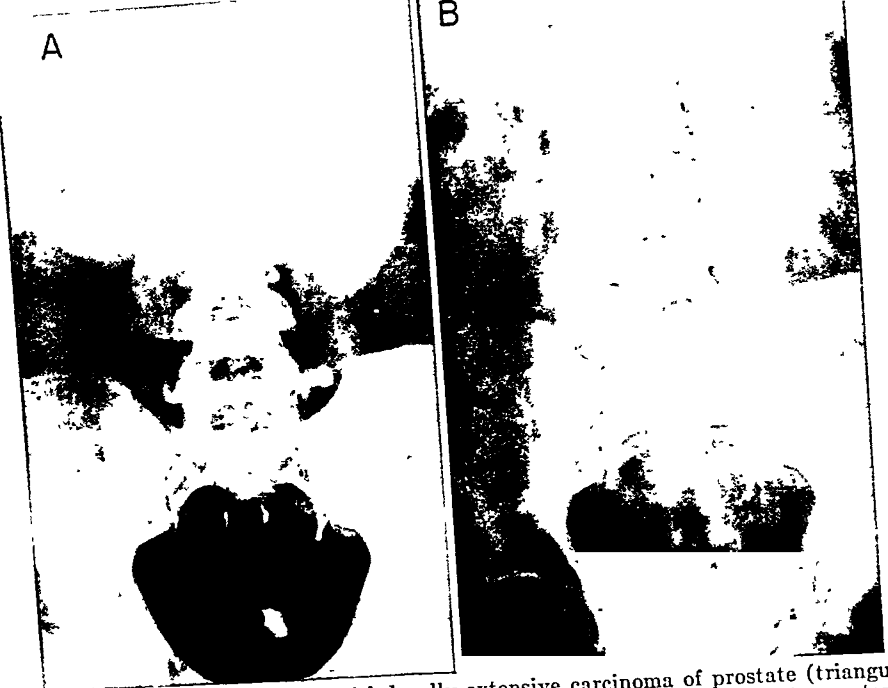
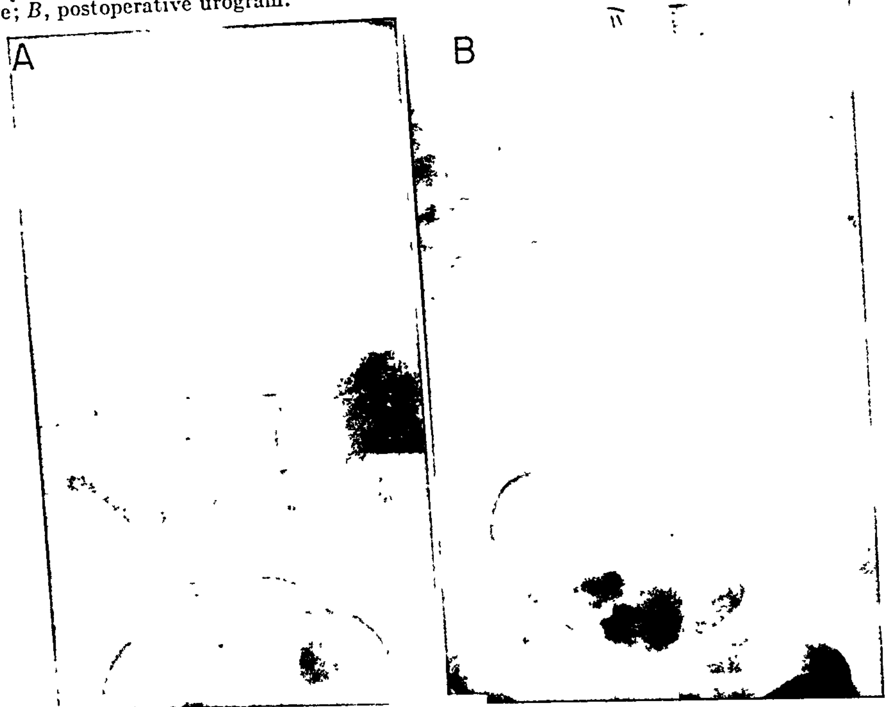


FIG. 7. Case 3. Man aged 61 with locally extensive carcinoma of prostate (triangular ligament involved). No apparent response to estrogen therapy. Bilateral uretero-enterostomy and radical prostatocystectomy with excision of triangular ligament. *A*, preoperative; *B*, postoperative urogram.



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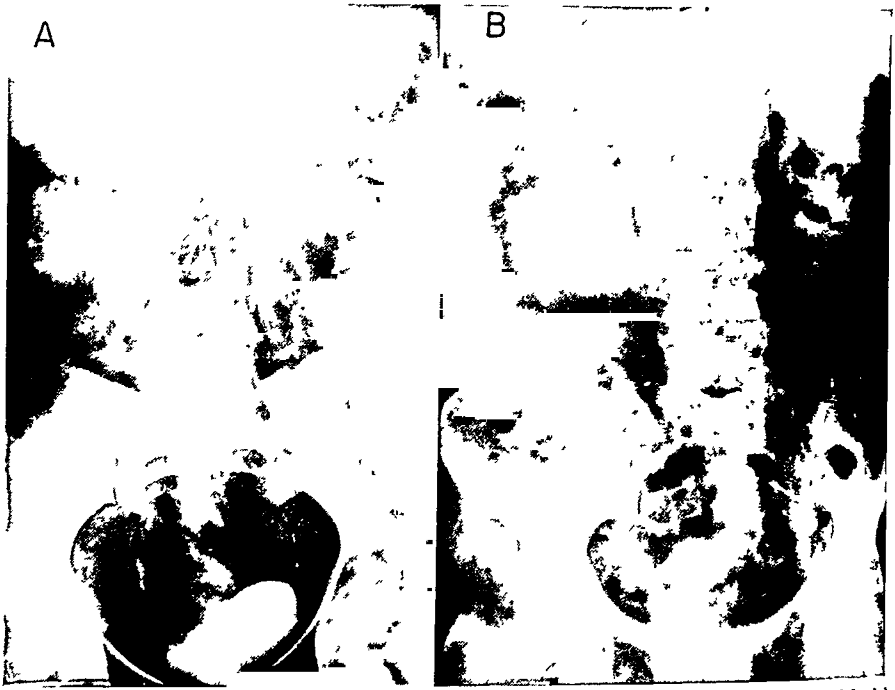


Fig. 9. Case 5. Woman aged 58 years with extensive infiltrating carcinoma of bladder *A*, filling defect in bladder and also changes in kidneys with loss of cortex suggestive of chronic pyelonephritis. Small calculus in lower calyx of left kidney observed in dye. Bilateral uretero-enterostomy and radical cystectomy. *B* (film transposed) shows postoperative urogram Stone in lower calyx of left kidney subsequently passed

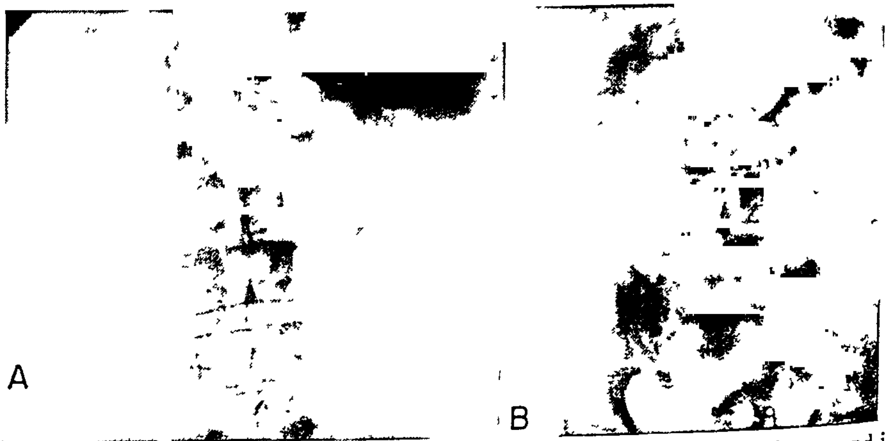


Fig 10 Case 6 Man aged 55 years with locally extensive prostatic carcinoma and involvement of triangular ligament. Bilateral uretero-enterostomy and cystectomy together with excision of triangular ligament *A*, preoperative; *B*, postoperative urogram

passed a small stone from the left kidney during the postoperative period. In no case has there been a significant elevation of nonprotein nitrogen Mild acidosis has been noted in most of the cases. Excretory urograms obtained early in the postoperative period have shown either no hydronephrosis and hydro-ureter or slight hydronephrosis and hydro-ureter, except in 1 case where moderately severe dilatation of renal pelves and ureters was noted on both sides. In that case we were not satisfied with the conduct of the operation. The patient was quite obese and difficulty was encountered in securing proper alignment and positioning of the ureters. In spite of the hydronephrosis and hydro-ureter, the patient is doing very well thus far, has had no febrile episodes, and has been completely relieved of her symptoms due to interstitial cystitis. Results from this procedure have been the best obtained by the author. Figures 5, 6, 7, 8, 9, 10, and 11 show the pre- and postoperative urograms obtained on the 7 surviving patients. Follow-up is limited to less than a year, but late follow-up studies will be reported subsequently. Whether the method itself is responsible for the results or whether my own greater experience with the general problem of uretero-enterostomy is the answer, it is impossible to know.

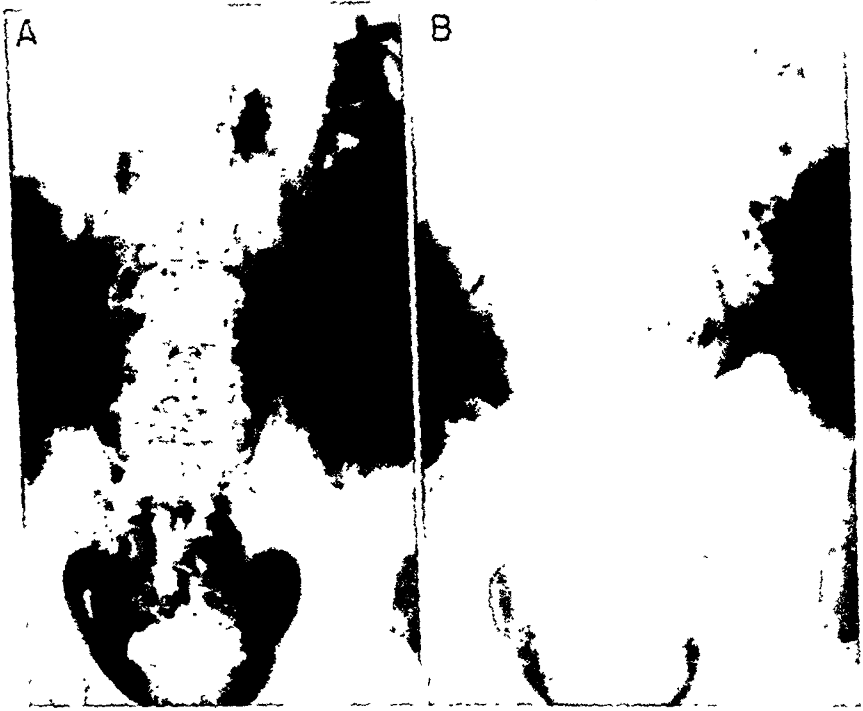
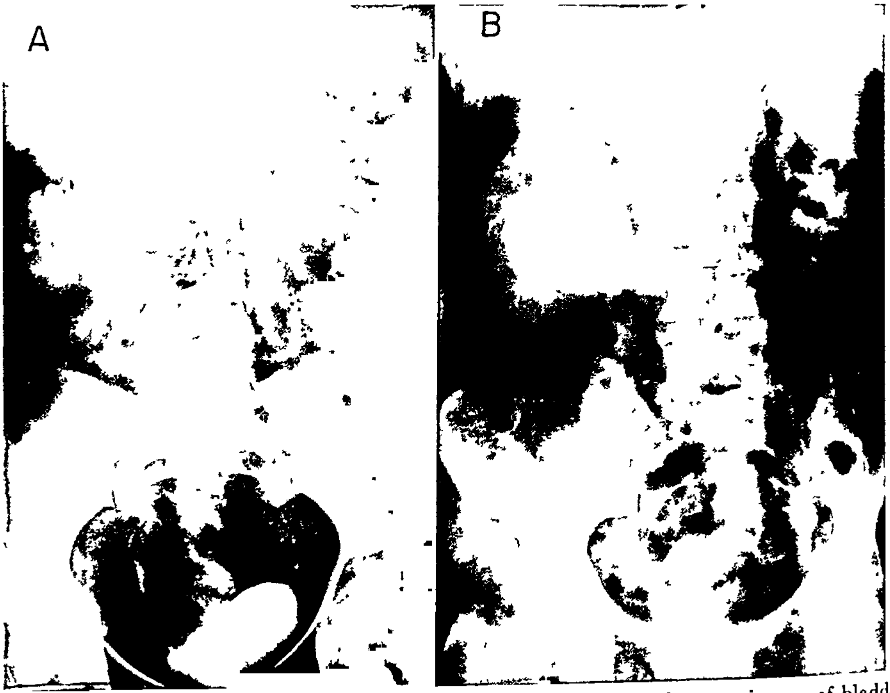


FIG. 11. Case 8. Man aged 58 years with locally extensive prostatic carcinoma which failed to respond to 6 months' estrogen treatment. Bilateral uretero-enterostomy and radical prostatocystectomy done. *A*, *preoperative*; *B*, postoperative pyelogram.

CONCLUSION

Several points in technique are discussed which seem to show that the direct anastomosis technique, as practiced by Nesbit and Cordonnier, is likely to eliminate some of the factors which lead to poor results from uretero-enterostomy.



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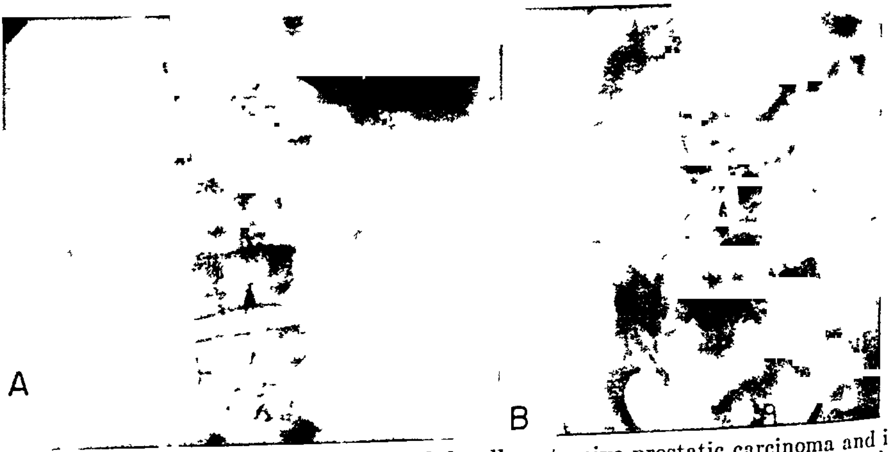

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ELECTROLYTE IMBALANCE FOLLOWING BILATERAL URETEROSIGMOIDOSTOMY

HERBERT S. DOROSHOW

The first successful uretero-intestinal transplantation was performed in 1892 for a ureterovaginal fistula. Since that time many excellent reports on the surgical approach to this problem have appeared in the literature. Emphasis has been placed on the eradication of such postoperative complications as stenosis at the site of neo-anastomosis with resultant obstructive uropathy, ascending infections to the kidneys, and peritonitis. In 1917, Baird, Scott and Spencer anastomosed the ureteral stump to the duodenum through the opening of the pancreatic duct. This was an attempt to avoid infection caused by opening the bowel. The urine was almost completely reabsorbed; the nonprotein nitrogen was markedly elevated; and death resulted in a few days.

Bollman and Mann in 1927 reported the effects of ureteral transplantation to various levels of the intestine on the nitrogenous constituents of the blood. The higher the level of the intestine used, the more rapid was the rise of the blood urea. When the ureters were transplanted into the rectum, a temporary elevation of the blood urea was encountered. At no level was an elevation of blood creatinine noted. This implied that the apparent changes were based more on selective reabsorption by the bowel rather than secondary renal damage.

In 1940, Jewett in a preliminary report on his two-stage operative technique indicated that significant reabsorption of the urine occurred in the rectosigmoid when emptying of the bowel was impaired or delayed. Dogs failing to void postoperatively promptly developed blood urea elevations. Posterior incision through the anal sphincter allowing more adequate bowel evacuation produced steady improvement. A later report (1944) by Jewett recorded the presence of recurrent acidosis with transient azotemia in a patient who failed to evacuate his bowel promptly.

Alterations in the plasma carbon dioxide combining power, chlorides and blood urea are known to occur in the face of renal damage. The relationship between these electrolyte alterations and urinary diversion to the bowel in the apparent absence of renal impairment has found little discussion in the literature. In June 1949, Ferris and Odel of the Mayo Clinic presented the first significant report on this subject. Their study was based on 141 cases of uretero-intestinal implantation, 83 per cent of which were performed for vesical carcinoma. Of their series 79 per cent manifested some degree of hyperchloremia (plasma chloride values above 103 meq/li), and 80 per cent developed plasma carbon dioxide combining power values below 50 volumes per cent or 23 meq/li.

Our attention was first acutely drawn to this problem in 1945. A 6 year old male child with bladder exstrophy and epispadias was admitted to the Brady Urological Institute, Johns Hopkins Hospital on May 19, 1945. On June 23,

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Hot Springs, Va., March 24, 1950.

In order to avoid the possibility of reflux of gas and feces from the bowel, particularly in the case of dilated ureters, it is suggested that the tunnel technique may be necessary, and in any case does no harm unless it can be shown that it inevitably leads to stricture of the ureter in its passage through the bowel wall.

A method of uretero-enterostomy is presented which combines the principle of direct anastomosis of the ureter to mucosa of bowel together with the formation of a submucosal tunnel.

This method has been utilized in the performance of uretero-enterostomy on eight patients. The results have been good to excellent.

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ELECTROLYTE IMBALANCE FOLLOWING BILATERAL URETEROSIGMOIDOSTOMY

HERBERT S. DOROSHOW

The first successful uretero-intestinal transplantation was performed in 1892 for a ureterovaginal fistula. Since that time many excellent reports on the surgical approach to this problem have appeared in the literature. Emphasis has been placed on the eradication of such postoperative complications as stenosis at the site of neo-anastomosis with resultant obstructive uropathy, ascending infections to the kidneys, and peritonitis. In 1917, Baird, Scott and Spencer anastomosed the ureteral stump to the duodenum through the opening of the pancreatic duct. This was an attempt to avoid infection caused by opening the bowel. The urine was almost completely reabsorbed; the nonprotein nitrogen was markedly elevated; and death resulted in a few days.

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1945 a right ureterosigmoidostomy was performed. On July 11, 1945, the left ureter was transplanted, and thereafter he developed anorexia and increasing restlessness. The second postoperative course was stormier. Since he had been an uncooperative, irascible patient preoperatively, it was difficult to ascertain what degree of this restlessness was based on his uncooperative attitude. Blood urea determinations throughout were within normal limits. A chloride determination on July 16, 1945 was reported as 89 meq/li. On July 17, 1945, he received 300 cc of $\frac{1}{6}$ molar lactate solution, 500 cc blood and 250 cc of saline intravenously. There was a temporary response, but a week later the child became increasingly fretful, irritable and developed nausea and vomiting. Unfortunately plasma chloride and CO_2 combining power values were not determined during this period. On the morning of August 2, 1945 a blood urea and CO_2 combining power were drawn. At 9:45 a.m., the child developed a sudden convulsion and stopped breathing. An autopsy revealed no dilatation of the left ureter and pelvis, moderate dilatation of the right ureter, and a normal right pelvis. Later in the day the laboratory reported a normal blood urea and a CO_2 combining power of 7.3 meq/li. It was apparent that the child had suffered an electrolyte defect postoperatively and eventually succumbed to an advanced acidosis.

TABLE 1

27865 B (F) CA BLADDER	SYMPTOMS	BUN	NPN (MG. %)	CO_2 c-p (MEQ/LI)	Cl (MEQ/LI)	UROGRAM
June 1944	Weakness Anorexia Confusion Generalized ache		38	14.1	117	Normal
Oct. 1944	Listless Generalized ache	0.28	48	13.6	117	
Dec. 1944	Semi-comatose Kussmaul breathing		42	7.8	125	Normal
July 1945	Semicomatose Nausea, vomiting Kussmaul breathing	0.32		14.1	105	Normal
	After treatment	0.28		27.6	100	

Bilateral ureterosigmoidostomy, first stage, Jewett, August 1940.
Bilateral ureterosigmoidostomy, second stage, Jewett, and total cystectomy, April 1941.

A second case, seen at the same time, was previously reported in 1944 by Jewett (table 1). This was a 50 year old man who had had a two-stage bilateral uretero-sigmoidostomy and total cystectomy for bladder carcinoma in 1940–41. He returned 3 years later, in June 1944, complaining of weakness, anorexia, mental confusion and generalized ache. His blood chemistries were reported as: nonprotein nitrogen 38, CO_2 c-p 14.1 meq/li, and Cl 117 meq/li. Excretory urograms showed normal functioning kidneys. His history revealed that he did not empty his bowels regularly, and that he voided per rectum 2–3 times a day. He was given intravenous lactate solution and rectal tube drainage to supply efficient bowel evacuation. There was a prompt clinical and chemical response, and the patient was advised to evacuate his bowels within 4 hour intervals. Nevertheless, he was readmitted twice during the last six months of 1944 in a similar condition. I first saw him in July 1945, when he was readmitted for the fourth time, semicomatose with Kussmaul breathing, and a blood picture of: blood urea nitrogen 0.32, CO_2 c-p 14.1 meq/li, and Cl 105 meq/li. The same treatment was instituted and his blood electrolyte pattern promptly resolved to: blood urea nitrogen 0.28, CO_2 c-p 27.6 meq/li, Cl 100 meq/li. He was discharged on oral sodium citrate. Eight months later he was readmitted in a similar condition, but thereafter he was followed periodically in the out-patient department until May 1947, and was apparently well controlled by oral alkali supplementation.

Both of these examples revealed postoperative blood chemical alterations manifested by severe clinical reaction. It was therefore interesting to note that investigation of other postoperative, unsuspected cases revealed similar electrolyte changes of varying degrees, namely: 1) blood urea elevation, 2) a plasma chloride elevation, and 3) an alkali deficit manifested by a diminished plasma carbon dioxide combining power.

The mechanism by which these alterations occur, in the apparent absence of renal impairment, is not entirely understood. During the normal metabolic processes of the body, alkaline and acid products are taken up by the blood stream. In certain diseases like diabetes an excessive amount of abnormal acid constituents are produced. The reaction of the blood is protected principally by three lines of defense, namely: 1) the buffer systems, 2) excretion of excess CO_2 by the lungs, and 3) excretion of fixed acids by the kidneys.

The carbonic buffer system is the most efficient blood control. Therefore, for the sake of simplicity it will be used in the modified scheme of table 2 to explain acid-base balance alterations. Since respiratory ailments are not involved in this study, the effects of lung control may be set aside.

In the development of metabolic acidosis, an increase in blood chlorides affords less available sodium for plasma sodium bicarbonate with a consequent fall in the alkali reserve. A relative deficiency of sodium exists. A loss of base or sodium provides an absolute sodium deficiency, and the same effect of a lowered CO_2 combining power is observed.

In this series, 70 per cent of those cases revealing electrolytic changes developed hyperchloremia. Ferris and Odel advanced the hypothesis that urinary chlorides are reabsorbed across the rectal mucosa producing a "hyperchloremic acidosis." This is an excellent observation, but it may not be the only agent involved. Selective reabsorption by the bowel is no doubt a primary factor since the described electrolyte defect apparently does not occur in cases of bilateral cutaneous ureterostomies.

Of the cases in this study with an altered electrolyte pattern, 55 per cent developed diarrhea. Ferris and Odel described the bowel sequence of events as retention with reabsorption of the urinary chlorides, followed by "hyperchloremic acidosis", which in turn produced a clinical syndrome including diarrhea. Part of their therapy was rapid and immediate bowel evacuation to diminish the amount of chloride reabsorption. It might be logical to wonder if the frequency and diarrhea state exhibited by these patients is not comparable to therapeutic, rapid bowel evacuation. If so, the rapidity of chloride reabsorption should certainly be diminished, and in time the condition should improve spontaneously. The questions remain: Is the diarrhea primary or secondary to the electrolyte defect observed? Base is lost through the bowel in diarrhea. Is there an analogous, significant base loss in these cases with bowel urinary frequency?

No doubt there are other factors involved in the selective reabsorption by the bowel. Increased intestinal fermentation may account for increased acidity of the bowel contents. The reabsorption of these products, and the reabsorption of urinary organic acid constituents may add to further the acid-base imbalance of the body.

TABLE 2

The Carbonic buffer system—most effective blood control

$$\frac{H.HCO_3}{NaHCO_3} = \frac{1}{20}\text{—Normal blood ratio}$$

RESPIRATORY (Changes in $H\cdot HCO_3$)

1. Impairment of breathing—retention of CO_2
   $\rightarrow \uparrow H\cdot HCO_3$—Respiratory Acidosis $\rightarrow$ compensatory rise in base which may give $\uparrow CO_2$ c-p
2. Increased Respiratory Rate (Fever) $\rightarrow$ loss CO_2
   $\rightarrow \downarrow H\cdot HCO_3$—Respiratory Alkalosis $\rightarrow$ compensatory drop in base which may give $\downarrow CO_2$ c-p

METABOLIC (Changes in $NaHCO_3$)

$[Na^+] = [HCO_3^-] + [Cl^-]$

$[Na^+] + [Cl^-] + [HCO_3^-] = K$

$\uparrow Cl^- \rightarrow \uparrow NaCl \rightarrow \downarrow NaHCO_3$—acidosis

Relative deficiency base $\rightarrow \downarrow CO_2$ c-p

$\downarrow Na^+ \rightarrow \downarrow NaHCO_3$—acidosis

Absolute deficiency base $\rightarrow \downarrow Co_2$ c-p

An attempt has been made in this study to eliminate renal impairment as a causative agent. Only those cases which have shown no postoperative obstructive or functional renal alterations, determined by excretory urography and the absence of active pyelonephritis, have been included in the study group. Of this group 38.5 per cent developed the electrolyte defect, which adds further credence to the theory that the predominant mechanism lies within the bowel. Nevertheless, this selection of cases is arbitrary, and does not completely remove the possibility of low grade tubular damage not evidenced by urography. If this is true, such functions of the kidney as base conservation by the conversion of di-sodium acid phosphate to mono-sodium acid phosphate said to occur in the

TABLE 3. *Bowel habits*

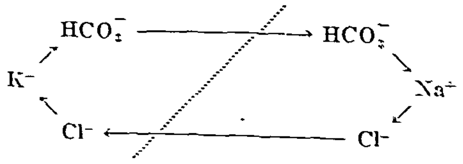
	N	%/20	%/52
DIARRHEA	11	55.0%	21.0
Transient azotemia with acidosis	1	5.0%	1.95
Acidosis alone	2	10.0%	3.85
Acidosis plus hyperchloremia	6	30.0%	11.85
Acidosis, azotemia plus hyperchloremia	2	10.0%	3.85
Total	11	55%	21.10
Azotemia	3	15%	5.8
Acidosis	11	55%	21.1
Hyperchloremia	8	40%	15.4
RETENTION			
Acidosis, azotemia plus hyperchloremia	1	5%	1.9
NORMAL bowel habits	8	40%	15.4

TABLE 4. *Possible factors in mechanism of electrolyte defect*

A. BOWEL
- 1. Selective reabsorption
  - a. Chlorides (Ferris and Odel)
  - b. Acids
    - (1) ↑ Intestinal Fermentation → ↑ Acid in bowel contents
    - (2) Urinary Organic Acids
  - c. Urea—influenced by urea splitting organisms in bowel
- 2. Bowel Habits
  - a. Diarrhea—loss of base through bowel, dehydration
  - b. Retention → ↑ Reabsorption
    Possible renal damage—ascending infection, obstruction

B. KIDNEY (Minimal tubular damage infection, obstruction)
- a. Loss Base (Normal mechanism below upset)
  - (1) $Na_2HPO_4 \rightarrow NaH_2PO_4 + Na^+$ (retained)
  - (2) $NH_4^+ + NaA \rightarrow NH_4A + Na^+$ (retained)
- b. Carbonic Anhydrase Mechanism in tissue capillaries upset (Hartman)

$$CO_2 + H_2O \xrightarrow{C—A} H \cdot HCO_3$$
$$H_2CO_3 + KHb \rightarrow HHb + KHCO_3$$



distal convoluted tubules, and the production of ammonia to replace the sodium in the urinary salts may be altered.

Hartman has verbally suggested the further possibility of disturbance of the carbonic anhydrase mechanism in the tissue capillaries by low grade renal damage. Carbonic anhydrase is an important factor in the production of H·HCO$_3$ from water and carbon dioxide. Normally HCO$_3^-$ produced joins the sodium in the extracellular fluid with a corresponding chloride shift into the intracellular fluid. A diminished intracellular production of the H·H^{CO_3} therefore affords less available extracellular sodium bicarbonate and a relative rise of the extracellular chlorides.

TABLE 5

Dog 1

	DAYS	REMARKS	NPN (MG. %)	Cl (MEQ/LI)	CO$_2$ (VOL. %)	WEIGHT
Pre-Op.	−11		42	110.7	48	13 kg.
	−7		35	109.9	46	
	−5		39	106	44	
Operation	0	U-S, bilateral				
		Rt. T-tube open				13.5 kg.
Post-Op.	2		30	94.6	39	
	7		40	111.6	34	
	9		38	112	29	
	11		35.8	107	41	12 kg.
	14		31.4	106	39	
	17	T-tube clamped	31.6	108	37	11.5 kg.
	21		46	115	22	
	23		41.5	118	23.5	
	33		45	112	30.5	10.5 kg.
	49		51	121.4	31.2	10 kg.
	53	After treatment	42	114.2	37.5	
	61		40	110.9	45.6	11 kg.

* Autopsy—No evidence of obstructive uropathy.

Dog 3

	DAYS	REMARKS	NPN (MGM. %)	Cl (MEQ/LI)	CO$_2$ (VOL. %)
Pre-Op.	−2		36.5	108	48.5
Operation	0	U-S, bilateral			
Post-Op.	1		38.4	112.3	50
	5		42	110	42.5
	10		42	114	39
	20		41.9	119.6	33.5

On 22nd p.o. day, injured in fight with another dog. Sacrificed. No evidence of obstructive uropathy.

The possible factors involved in the mechanism of the electrolyte defect are listed in table 4. While the theory of chloride reabsorption of Ferris and Odel is logically drawn, it is possible] that more than one factor is involved in the changes noted.

Five dogs were transplanted bilaterally according to the technique of Davalos. Dog 3 was severely injured in a fight with another dog and was sacrificed on the twenty-second postoperative day. At that time he had already manifested a slight elevation of blood nonprotein nitrogen and plasma chlorides and a drop in the plasma CO_2 c-p. Only dog 1 was suitable for study (table 5). Both ureters were transplanted to the bowel. A T-tube was placed in the right transplanted ureter and the outer arm allowed to drain until the seventeenth postoperative day. According to Van Slyke and Evans, the normal plasma chloride value for the dog is 105 to 115 meq/li. With this in mind, it is apparent that there was no appreciable change in the nonprotein nitrogen or plasma chlorides. Yet there was a slight tendency for the CO_2 c-p to fall. As soon as the T-tube was clamped, all the urine was diverted to the bowel, and there was an associated rise in nonprotein nitrogen and plasma chlorides, and a further drop in the CO_2 c-p. On the forty-ninth postoperative day, treatment consisting of the administration of intravenous saline and molar lactate solution was instituted. There was a prompt response in the electrolyte pattern.

TABLE 6. *115 cases ureterosigmoidostomy, Brady Urological Institute, Johns Hopkins Hospital (63 cases eliminated)*

1. Postoperative obstructive uropathy
   a. Roentgenography
   b. Retention of NPN wastes
2. Secondary infection → renal impairment
3. Inadequate chemical study or follow up
4. Immediate postoperative death

52 cases suitable for study

48%—Normal chemistries
52%—Chemical imbalance
    38.5%—No x ray evidence obstructive uropathy
    13.5%—Minimal to moderate x-ray changes (adequate drainage, no active infection, azotemia transient)

With outer drainage from the T-tube in the right ureter, the fall in the CO_2 c-p, with no appreciable chloride elevation, could have been influenced by 1) reabsorption of acids from the urine diverted to the bowel and those produced by any increased intestinal fermentation, and/or 2) loss of base from the bowel. The outer arm of the T-tube clamped, and all the urine diverted to the bowel, may have increased the degree of chloride reabsorption setting the mechanism of "hyperchloremic acidosis" into play.

Of 115 cases of bilateral ureterosigmoidostomy done at the Brady Urological Institute, Johns Hopkins Hospital since 1941 (table 6), 52 cases were found suitable, and fulfilled the basic criteria for this survey. These are referred to as the study group. Sixty-three cases were eliminated because of obvious obstructive uropathy, active infection, inadequate chemical study and follow-up, and immediate postoperative death. Of the study group 82.7 per cent were operated on for vesical carcinoma (table 7).

Of the 52 cases remaining, 48 per cent had normal chemistries. Two of these were treated prophylactically with alkali. Whether they would have developed electrolyte imbalance is impossible to ascertain.

Seven cases showing minimal to moderate postoperative urogram changes, but having adequate drainage and no active secondary infection, were included in the total number of study cases, but not in the calculated percentages of chemical change. These comprised the remaining 13.5 per cent. The actual percentage of cases with electrolyte defect in this group caused by renal damage or by urinary diversion to the bowel alone cannot be determined.

TABLE 7. *Diagnoses*

DIAGNOSIS	NO. CASES	% 52 CASES
Vesical carcinoma	43	82 7
Exstrophy of the bladder	6	11.5
Traumatic rupture of urethra	2	3.85
Incrusted panmural cystitis	1	1.95
Total . ..	52	100.00

TABLE 8

	20 CASES NO X-RAY CHANGES			7 CASES MINIMAL TO MODERATE X-RAY CHANGES (ADEQUATE DRAINAGE, NO ACTIVE INFECTION)			
ELECTRICAL CHANGES	#	%/20 Cases	%/52 Cases Study Group	#	Total 20 plus 7	%/27 Cases	%/52 Cases Study Group
Transient azotemia with acidosis	2 (1)*	10	3.85	0	2	7.4	3.85
Acidosis alone	4 (2)*	20	7.7	1*	5	18.5	9.6
Acidosis plus hyperchloremia	8	40	15.4	1	9	33.3	17.3
Azotemia plus acidosis and hyperchloremia	6	30	11.55	5	11	40 7	21.15
Total	20	100	38.50	7	27	99.9 (100)	51.9 (52)
Azotemia	8	40	15 4	5	13	48.1	25
Acidosis	20	100	38.5	7	27	100	51.9
Hyperchloremia	14	70	26 95	6	20	74.0	38.5

* Inadequate Cl study.

Twenty cases (38.5 per cent) with no x-ray evidence of obstructive uropathy revealed electrolyte aberrations (table 8). Of these, 100 per cent developed mild to severe, recurrent acidosis; 40 per cent were associated with transient azotemia; and 70 per cent revealed hyperchloremia. The over-all percentages are definitely lower than those reported by Ferris and Odel. This may, in part, be due to the fact that an attempt was made in this study to eliminate those cases with obstructive changes, all of which developed chemical alterations.

The onset of the electrolytic change varied widely between 3 days and 3 years, and no doubt was partly influenced by the postoperative administration of intravenous fluids and alkali in conjunction with sulfonamide therapy. The most frequent time of onset in the study group was between 14 and 30 days (table 9).

Clinical signs were revealed by 11 cases (21 per cent) of the study group and for the most part were mild (7 cases). Three patients exhibited severe clinical reaction, and one case terminated in an acidotic death. The symptoms manifested were anorexia, weakness, lethargy, weight loss, diarrhea, dizziness, nausea and vomiting, restlessness and irritability, Kussmaul breathing, confusion, and a semicomatose state.

Twenty-seven cases with the electrolyte defect were treated with alkali. All responded to the treatment. The amount of effective bicarbonate or sodium citrate varied with the individual response, and was controlled by the effect on the electrolyte pattern. In those cases with severe clinical manifestations, intravenous molar lactate augmented the therapy.

TABLE 9 *Onset electrolytic change*

Average	14–30 days (Influenced by p o fluids)
Longest	3 years
Shortest	3 days

Clinical signs

	#	% 20 cases	% 52 cases
Exhibited	11	55%	21.0
Mild	7	35%	13.4
Severe	3	15%	5.8
Death	1	5%	1.9

SUMMARY

A blood electrolyte alteration is known to complicate cases of urinary diversion to the rectosigmoid. An arbitrary attempt was made to rule out renal impairment as a causative agent, making only 52, out of 115 cases of bilateral ureterosigmoidostomy investigated, available for study. Of the study group 48 per cent had normal blood chemistries; the remaining cases revealed the chemical aberrations of a transient azotemia, acidosis and hyperchloremia.

Of the patient study group 21 per cent developed varying degrees of clinical reaction manifested by weakness, anorexia, weight loss, diarrhea, nausea, vomiting, irritability and confusion. One case terminated in an acidotic death.

Ureterosigmoidostomy was done on 5 dogs (Davalos technique), and one showed characteristic changes. Another began to manifest the blood chemical changes, but had to be sacrificed before adequate study was complete.

The exact mechanism of the alterations noted is not completely understood. It is believed to be due to the following factors working singly or in combination: 1) bowel reabsorption of the urinary products (chlorides, acids and urea) and intestinal ferments, 2) diarrhea producing base loss from the bowel, and 3) questionable low grade, renal tubular damage upsetting the base conservation properties of the kidney.

All patients treated with oral or intravenous alkali showed an immediate improvement with a return of plasma bicarbonate, chlorides and blood nonprotein nitrogen to normal levels.

It is apparent that ureterosigmoidostomy, previously considered successful when secondary obstructive uropathy and infection were avoided, presents an additional chemical hazard, which cannot be underestimated and requires thorough postoperative investigation.

I would like to thank Dr. William Wallace Scott of Baltimore for making many of these Brady Clinic cases available for study, and Dr. David M. Davis of Philadelphia for making the animal experimentation possible.

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REFERENCES*

BAIRD, J. S., SCOTT, R. L. AND SPENCER,: Studies on transplantation of the ureters to the intestine. Surg., Gynec. & Obst., **24:** 482, 1917.

HINMAN, F. AND BELT, E.: Experimental study of ureteroduodenostomy. J. A. M. A., **79:** 1917, 1922.

BOLLMAN, J. L. AND MANN, F. C.: Nitrogenous constituents of blood following experimental transplantation of ureters into different levels of intestine. Proc. Staff Meeting Mayo Clinic. June 15, 1927.

GEER, W. A. AND DRAGSTEDT, L. R.: Effects of deviation of urine to the blood stream and intestines of dogs. Ann. Surg., **108:** 263-270, 1938.

JEWETT, H. J.: Uretero-intestinal implantation: Preliminary report. J. Urol., **44:** 223-226, 1940.

JEWETT, H. J.: Uretero-intestinal anastomosis in two stages for cancer of the bladder: Modification of original technique and report of 33 cases. J. Urol., **52:** 536-562, 1944.

FERRIS, D. O. AND ODEL, H. M.: Observations of the electrolyte pattern of the blood after bilateral ureterosigmoidostomy. Read at meeting, Section of Urology, American Medical Association, Atlantic City, N. J., June 8, 1949; J. A. M. A., **142:** 634, 1950.

DARROW, D. C.: Disturbances in electrolyte metabolism in man and their management. Bull. N. Y. Acad. Med., **24:** 147-165, 1948.

GAMBLE, J. L.: Extracellular fluid; Renal defense of extracellular fluid. Bull. Johns Hopkins Hosp., **61:** 174, 1937.

DARROW, D. C.: Body fluid physiology; relation of tissue composition to problems of water and electrolyte balance. New Eng. J. Med., **233:** 91, 1945.

DAVALOS, A.: New technique of simultaneous bilateral ureterointestinal anastomosis; Report of experimental study. J. Urol., **54:** 357-367, 1945.

VAN SLYKE, K. K. AND EVANS, E. T.: Paradox of alkalosis caused by hypochloremia. Ann. Surg., **126:** 545-567, 1947.

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* Arranged chronologically.

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CARCINOMA OF THE BLADDER: A CORRELATION OF PATHOLOGY WITH TREATMENT AND PROGNOSIS

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The indications for the various procedures used in the treatment of bladder tumors have never been clearly defined. Uncertainty as to whether local destruction, segmental resection or cystectomy should be performed suggests that past indications have an insecure basis. Although some tumors have been controlled by these methods, many have not been cured. The indications for total cystectomy especially need clarification.

Invasion of the underlying muscle, as Jewett has said,[1] is an important feature of bladder tumors. On this fact, we believe, can be based intelligent treatment and more accurate prognosis. Muscle invasion may provide a better basis for treatment than indications previously given by ourselves and others.[2]

With these problems in mind, we have reviewed 700 cases of carcinoma of the bladder treated at the Massachusetts General Hospital from 1934 to 1949. These tumors were studied to find out why some were easily cured and others were not. A review of their microscopic characteristics indicated that penetration into the bladder muscle might have more significance than the size, grade, or location of the tumor and whether it was papillary or nonpapillary. *Any type* of tumor can invade the muscle and be termed infiltrating. We have tried to determine whether there is a correlation between muscle invasion of a tumor and the choice of treatment and prognosis.

The only tumors studied were those that provided us with sufficient material to give microscopic evidence that muscle invasion was or was not present. Clinical impressions of tumor invasion were considered inaccurate. Over-all statistics of cure have little value and are not included. The tumors of patients who could not be followed or who died in the hospital were omitted. The remaining tumors constitute a small group but they form a sound basis for study since the end results are known and the tissue was secured by segmental resection, total cystectomy or from neoplasms from which deep and adequate biopsies had been secured. Biopsies from the periphery of a tumor may be misleading particularly regarding tumor penetration. One hundred and thirty-five tumors with adequate pathological sections and follow-up were suitable for study.

From 1934 to 1949, ninety-eight total cystectomies for cancer of the bladder were done at the Massachusetts General Hospital. Eighteen of these patients

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Read at annual meeting, American Urological Association, Washington, D. C., May 30, 1950.

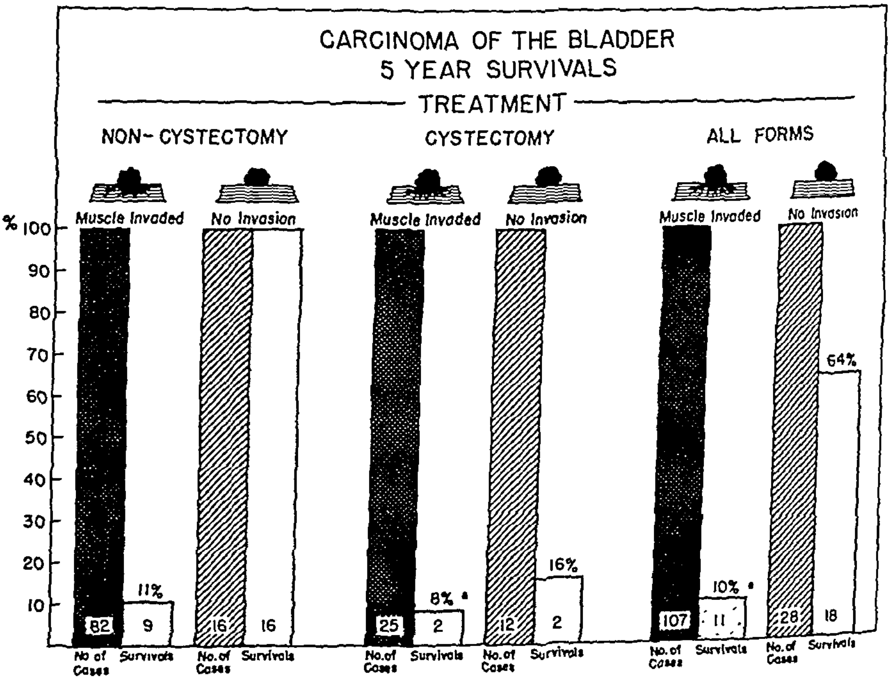
This study was aided by an Institutional Grant from the American Cancer Society to the Massachusetts General Hospital.

[1] Jewett, H. J. and Strong, G. H.: Infiltrating carcinoma of the bladder: Relation of depth of penetration of the bladder wall. J. Urol., 55: 366–372, 1946.

[2] Kerr, W. S. Jr. and Colby, F. H.: Pelvic lymphadenectomy and total cystectomy in the treatment of carcinoma of the bladder. Tr. Am. Assn. Genito-urin. Surg., 41: 57–66, 1949.

died in the hospital, an operative mortality of about 20 per cent. Of the remaining 80 cases, *2 could not be followed, 33 were too recent to be of value* and in 8, pathological material was not satisfactory. Thirty-seven cases of total cystectomy are included in the study.

Invasion of the regional lymph nodes by cancer of the bladder requires serious consideration. The tendency for these tumors to invade the lymphatics depends upon invasion of the deep layers of the bladder wall since there are no lymphatics in the mucosa. As far as we know, no tumor in this series *that did not invade the muscle* involved the regional lymph nodes. Forty per cent of fifteen tumors that did invade the muscle and which were treated by cystectomy and pelvic lymphadenectomy involved the regional lymph nodes. Unless these lymph nodes are removed at the time of partial or total cystectomy, many of these patients are given no chance of cure.



* 2 CASES WITH BONE METASTASES AT 6 YEARS

FIG. 1

The charts illustrated in figure 1 depict the results of treatment and the importance of tumor invasion of the bladder muscle. The first chart shows the 5-year survival rates of patients who left the hospital alive and who were *treated by methods other than cystectomy*. Eighty-nine per cent of the 82 patients whose tumors invaded the muscle were dead at the end of 5 years, on an average of 11 months after operation. As far as we could determine, they all died of cancer. Nine or eleven per cent were alive and well.* When the tumors *did not invade* the bladder muscle, the situation was different. All 16 patients were alive and well 5 years after operation.

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* Seven were treated by subtotal resection.

In the second chart are shown the 5-year survival rates of patients whose tumors were treated by cystectomy. Only two, or 8 per cent of the 25 patients whose tumors invaded the muscle were alive. Both of these patients developed bony metastases at 6 years and 1 has died. The 23 patients who died survived operation for an average of 10 months. Nineteen of them, we know, died of cancer or the effects of operation. Two died from causes apparently unrelated to their tumors and the cause of death in 2 was not determined. Five-year survivals of the 12 patients whose tumors did not invade the muscle and who were treated by cystectomy were 2, or 16 per cent. Of the 10 deaths in this group, 5 were from uremia, 1 from a cerebral accident, 1 from pneumonia and 3 from uncertain causes.

The third chart is a combination of the two previous charts and shows the 5-year survival rate when all forms of treatment were employed. When the tumors invaded the muscle only 11 patients survived for 5 years. This is 10 per cent of 107 patients. The end result, therefore, for these patients was essentially the same, whether or not cystectomy was performed. In 28 patients, the tumors did not invade the muscle and 18, or 64 per cent of them survived for 5 years. Cystectomy for these patients, therefore, resulted in a lower 5-year survival rate than when cystectomy was not done. As far as we could tell, the invasive or noninvasive tumors treated by cystectomy were very similar to those treated by other methods.*

Our figures are based on a small group of tumors, but they are the result of a microscopic study of the invasive features of these tumors and as accurate a follow-up as possible.

CONCLUSIONS

Invasion of the bladder muscle is an important feature of bladder tumors. When there was no evidence of muscle invasion, the 5-year survival rate was 64 per cent and only 10 per cent when the muscle was invaded. The presence or absence of muscle invasion provides a guide to treatment and prognosis. Ade-

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*

	MUSCLE INVADED		NO INVASION	
	Cystectomy	Noncystectomy	Cystectomy	Noncystectomy
No of patients	25	82	12	16
Grade of tumor	%	%	%	%
Grade 2	24	19.5	8.3	6.2
Grade 3	76	80.5	91.7	93.8
Size of tumor				
1–3 cm	24	25.6	66.6	75
3 cm or over	76	74.4	33.4	25
Mean age in years	60 ± 1.5 (standard error of the mean	63 ± 1.1	57.3 ± 1.4	62 ± 2.5

When the muscle was invaded, these figures show no significant difference between tumors treated by cystectomy and tumors treated by other methods with respect to grade or size of tumor and age of patient. This is true also of the non invasive tumors that were treated by cystectomy or other methods.

quate biopsy must be obtained to determine whether or not the tumor invades the underlying muscle. Tumors that do not invade the muscle should be treated, if possible, by methods other than cystectomy. If the muscle is invaded, cystectomy may be considered. Tumors that invade the muscle are difficult to cure by any present methods of treatment.

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DISCUSSION

Dr. Lloyd G. Lewis (Washington, D.C.): Drs. Colby and Kerr have emphasized the importance of infiltration in relation to the prognosis of bladder cancer. I am sure no one will disagree. Dr. John T. Geraghty stressed infiltration in his classification of papillary tumors. The emphasis then shifted to grading by Dr. Broders. I believe that Dr. Jewett's contributions have brought out a more important item than infiltration; i.e., the necessity for study of the deeper tissues secured at biopsy or surgery. Whereas infiltration of the bladder wall can be regarded as a serious situation in the case of papillary carcinoma, which does not necessarily infiltrate, this factor is always present in the case of squamous or undifferentiated or adenocarcinoma. Infiltration may be a feature of the pathologic type or it may be a late manifestation of change in a previously less malignant tumor evidenced by squamous metaplasia or stromal invasion.

All surgery for bladder cancer must be regarded as insufficient because we do not remove the cause nor the source tissue completely. One of my total cystectomy patients recently died from a new growth of grade 2 tumor in the ureter 4 inches above the site of ureterosigmoidostomy 3½ years after surgery. There was no evidence of any lesion of either ureter preoperatively. Tumors of transitional epithelium may arise in or recur on the transitional epithelial surfaces of the kidney pelvis, ureter, posterior urethra or in the prostatic ducts.

Since we cannot eradicate the cause of the cancer nor eliminate the source tissue, treatment must be adequate to remove the local lesion and when indicated, the lymphatic drainage tracts. I believe that transurethral resection rather than fulguration of even the smallest noninfiltrating tumors should be done. Then we can study the tissues with the microscope and the base of the lesion is more liable to have been adequately treated. Segmental resection has its place. Lymph node resection, in my opinion, should be a part of the proceedure of total cystectomy.

Radiation can play a role in the treatment of bladder tumors. Certain fundamental principles must be followed: 1) The full lethal tumor dose for a given tumor must be administered. The more benign tumors require higher dosage than the most malignant infiltrating tumors. 2) The lethal tumor dose requirement for a tumor of a few cells is the same as for a bulky tumor of similar type. 3) The method of application must be selected to administer adequate dosage to the tumor bearing area while providing maximum protection to the surrounding structures, rectum, vagina etc. 4) The lethal tumor dose must be delivered in optimum time. Contact radiation produces necrosis. X-rays produce distal changes due to the slow rate of application. Dosage, even if inadequate, must not be repeated after a long delay. An interval of 6 months between treatments will result in slough of the previously damaged avascular tissues.

I am not so much worried about local recurrence of tumor after adequate resection as I am about recurrence of new tumor growth elsewhere in the bladder. We cannot adequately radiate the entire transitional epithelial system. The method of radiation of the bladder illustrated in the exhibit of Dr. Milton quate biopsy must be obtained to determine whether or not the tumor invades the underlying muscle. Tumors that do not invade the muscle should be treated. if possible, by methods other than cystectomy. If the muscle is invaded, cystectomy may be considered. Tumors that invade the muscle are difficult to cure by any present methods of treatment.

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Friedman and myself allows for radiation, not only of the site of the tumor but for the great part of the tumor bearing area of the bladder wall. It is recommended for treatment of multiple noninfiltrating tumors and for recurrent tumors. It has proved its value in cases of infiltrating cancer when surgery was refused or contraindicated. For idequate radiation by this method, the tumor must be thin or the bulk of the tumor removed. Radiation from a radium source decreases by approximately the square of the distance from the source. Radium, 25 mg. placed accurately at the center of a Foley balloon catheter inflated to 4 cm. diameter will deliver to the bladder wall in contact with the balloon at 2 cm. distance 100 r in 24 hours; at 3 cm., the area of muscularis and lymphatic tracts in the bladder wall 550 r per day.

I must emphasize the necessity for absolute accuracy in measurement of the distance from the source of radium to all points on the surface of the balloon. An error of 1 to 2 mm. will result in overdosage or underdosage up to 1000 r in 10 days. The position of the radium must be checked by x-rays.

DR. HUGH J. JEWETT (Baltimore, Md.): Dr. Colby has done us a service in presenting additional evidence to show that infiltration of the bladder wall is a bad sign. Furthermore, his forthright presentation of his material should dampen some of the ardor which exists today in certain sections of the country for routine cystectomies.

Paul Aschner, nearly twenty-five years ago, told us, after a careful study of 287 cases, that prognosis could not be determined by biopsy alone in cases of malignancy; that the presence or absence of infiltration was a far more reliable indication of the gravity of the situation.

The question which naturally arises is, Are all cases of infiltration hopeless? On the basis of 206 cases carefully studied by sections accurately made through the site of deepest penetration by the tumor, I believe we can say that the incidence of extravesical spread is directly proportional to the depth to which the tumor has penetrated the bladder wall. The next question then is, How deep does this infiltration have to be before extravesical spread occurs? This may vary somewhat with tumors of different grades of malignancy, but in the majority of cases, it would seem that the critical point is about halfway through the muscularis.

(Slide) These two bar diagrams indicate the percentage of patients with infiltrating carcinoma surviving 5 years or longer following cystectomy or segmental resection. In the first group, in which the infiltration was less than half way through the muscularis, 11 patients out of 12 survived 5 years or longer without any evidence of recurrence.

The second group represents those cases in which the tumor had gone more than halfway through the muscularis: Only 1 patient out of 45 had survived 5 years. If we lumped both of these two groups together, our figures would roughly parallel those of Dr. Colby.

I realize that our conclusions are only as valid as the facts on which they are based, and in this instance the facts are represented by a series of cases too small to be of much statistical significance. I nevertheless believe that there is definite indication that superficial muscular infiltration does not necessarily mean that metastasis has occurred, and that deep muscular infiltration usually means that metastasis has occurred. We will be obliged to await the accumulation of further material before we are able to state that these assumptions are scientifically correct.

(Slide) In the meantime, while we are awaiting the accumulation of that material, it seems advisable to segregate our cases clinically as accurately as we can, and we have found that a correlation of a properly taken biopsy with the bimanual pelvic examination gives us a tremendous amount of information. If there is no palpable thickening and no mass on pelvic examination, and a properly taken biopsy shows submucosal or muscular infiltration, we have reason to believe that the tumor is superficial and the outlook is good. If there is thickening of the bladder wall but no mass is palpable, and we see tumor cells in the muscle, we still believe that the infiltration is superficial and the outlook is good, provided that the local growth can be completely destroyed. In all other cases in which a mass is palpable, and biopsy shows the mass to be tumor, deep penetration has occurred and the outlook is poor, even with cystectomy.

Dr. Walter M. Kearns (Milwaukee, Wis.): Dr. Colby has presented an excellent review and added valuable information, along with that of Dr. Jewett, to our knowledge about the prognosis of carcinoma of the bladder. I would like to make this one point, about the use of the indwelling catheter at the time of anastomosis. To perform one-stage bilateral ureteral anastomosis, using the trough as in the Coffey 1 operation, without leaving an indwelling catheter in at least one side, places the patient in a precarious situation should postoperative obstruction develop.

In our last 12 cases we splinted both ureters. A 8F catheter carrying a 10F bulb was left in the right ureter, and passed out through a rectal tube. A 5F catheter is placed 15 cm. in the left ureter, the distal part curled up in the gut to be taken up later and passed in the fecal current.

It has passed from every patient except one about whom we became a little anxious on the nineteenth day. A proctoscope was used to remove it. (Slide) The looped catheter had decided to rest at the rectosigmoid elbow, but was easily extricated.

(Slide) Another patient on the second day, the catheter is demonstrated in the left renal pelvis. (Slide) On the thirteenth day it has moved to a lower level. On the fourteenth day the catheter is seen curled up in the rectum and later on this day it passed. (Slide) This 30 minute excretory urogram obtained on the same patient on the sixty-seventh postoperative day reveals a good anatomical result.

(Slide) The third patient is a woman who had a hysterectomy for large fibroids, but the surgeon also encountered carcinoma. He had great difficulty removing the uterus contending with a considerable amount of hemorrhage and in controlling it, managed to obstruct both ureters. She was anuric for 5 days. At cystoscopy it was impossible to pass a catheter more than 5 cm. on either side. A left nephrostomy was carried out. After another 9 days the nonprotein nitrogen level in the blood improved from 145 to 60 mg. per cent. Then bilateral ureteral intestinal anastomosis was performed. (Slide) On the second postoperative day 5 tubes shown in this roentgenogram are the Wangensteen tube in the stomach, the nephrostomy tube on the left, the bulbed ureteral catheter still in the right ureter, and the small No. 5 catheter still in the left ureter with distal end curled up in the sigmoid, and lastly, the rectal tube. The bulbed catheter is not as usual coursing through the rectal tube in this instance, because it was impossible to insert the rectal tube far enough to reach the level of the anastomosis at the time of operation. The previous hysterectomy had caused a sharp angulation. (Slide) The barium enema locates this angulation, and locates both catheters in the sigmoid. (Slide) On the sixth day the both catheters are still in the gut, and a pyelogram has been carried out through the nephrostomy tube on the left. On the seventh postoperative day both catheters were passed spontaneously, following a cathartic.

It is my firm belief that the insertion of a catheter on the right side is a prerequisite to avoid postoperative obstruction when the Coffey operation, employing a trough, is carried out. A smaller catheter placed in the left ureter gives added assurance. The catheters not only prevent angulation, but maintain drainage when edema or marked flatulence develops. Moreover, the splinting sets up the early fibrosis in the form of a straight channel and the late obstruction which often develops may very well be obviated.

Earlier, while using the two-stage Jewett technique we encountered one patient in whom complete obstruction of both ureters developed with anuria and azotemia. It was readily overcome at cystoscopy by the passage of ureteral catheters to the kidney pelves. This complication occurred when we observed every precaution to avoid it, and it is apt to occur following the one-stage operation. Obstruction then represents a grave complication in these exhausted patients with relief attainable only through nephrostomy drainage.

Dr. Walter S. Kerr, Jr. (Boston, Mass.): It has been noted that of 15 patients with infiltrating tumors who have been treated by cystectomy and pelvic lymphadenectomy six (40 per cent) have had microscopic evidence of metastatic disease in regional nodes. Although none of the patients in the 37 cases of cystectomy mentioned in this report had pelvic lymphadenectomy, further mention of this aspect of the treatment of carcinoma of the bladder should be made.

Two years ago, the dissection of the lymphatic tissue of the pelvis was added to the procedure of cystectomy in the hope that fewer patients would develop recurrences. Four of the patients with infiltrating tumors returned to the hospital on the average of 5 months after cystectomy and were explored. Three of these 4 patients were found to have recurrent disease and are now dead.

(Slide) The node dissection as originally performed included removal of the tissue along the lower half of the common iliac vessels, external and internal iliac vessels and in the obturator space. One patient had recurrent disease along the left common iliac vessels just below the aorta and around the left epigastric vessels, another had disease in the pelvis lateral to the rectum, and the third patient had recurrent tumor involving the left epigastric vessels and the peritoneum.

After these recurrences were found, the limits of the lymph node dissection were extended to include as much of the lymphatic bearing tissue in the pelvis from the lower portion of the aorta to the region of the rectum below the middle hemorrhoidal vessels. Patients who have had the more extensive operation have not been followed long enough to determine its efficacy. The one patient who did not have recurrence is alive without evidence of disease 21 months after operation. He did not have involvement of nodes.

If these patients develop recurrences in the pelvis, as I suspect they will, for one cannot do an adequate pelvic dissection without removing the rectum, we are faced with the same problem as the surgeons attempting to cure cancer of the stomach. Will the rate of survivals of cancer of the stomach be increased by methods similar to those of Mr. Allison of England, who dissects the mediastinum, does a total gastrectomy, removes the spleen and a large part of the pancreas in order to remove known sites of lymphatics draining the stomach? Will we be justified in removing the rectum in order to enable us to remove lymphatics to which bladder carcinoma may spread. I don't believe so, for it is likely that the mutilation of function, disability and the mortality and morbidity of such an extensive procedure will outweigh the occasional satisfactory result.

Dr. Paul W. Aschner (Brooklyn, N. Y.): As Dr. Jewett mentioned, I made a study of the subject with particular reference to biopsy 20 years ago. I wish again to stress that in deciding upon the form of therapy which should be used for a particular bladder tumor many factors require consideration. One of these is the pathology of the lesion as determined by cystoscopic, roentgen and clinical methods with reference to the question of infiltration, which is of great importance; the second is the cytology of the tumor.

In evaluating biopsy material, that which is obtained on a fulgurating electrode or a resectoscope loop is not dependable because of the dehydrating distorting effect of the electrocoagulating current. The use of the small cold biopsy forceps to obtain material from several parts of the tumor including its base, whenever possible, will often give information as to infiltration of submucosa or muscularis.

As to therapy, I believe it has been demonstrated by those with the largest experience in total cystectomy that when infiltration does not exist total cystectomy is rarely necessary, and per contra when deep infiltration exists one undertakes the radical procedure including lymph node dissection with the knowledge and the fear that it probably will be in vain.

The nature of bladder tumors is such that until we discover the agents which produce them from urothelium anywhere from the renal calyx all the way down into the urethra, all of similar types, we are still working on a practical basis and not on a truly scientific one.

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CUTANEOUS METASTASIS FROM CARCINOMA OF BLADDER

HOMER G. HAMER AND (by invitation) MYRON H. NOURSE

The recent finding of a subcutaneous nodule lying in the abdominal wall of a patient with carcinoma of the bladder which microscopically proved to be a metastatic lesion from the bladder, prompted a survey of the literature for similar instances. Eleven cases have so far been reported. The actual incidence is probably considerably greater than this would lead one to believe. Evidence, however, is lacking. Kretschmer seems to have demonstrated the first positive evidence of skin metastasis of one case in 1922. Rolnick and O'Neill in 1932 described skin metastasis from carcinoma of the bladder in a 48-year-old man. Atkinson in 1942 reported a case which developed a metastatic nodule on his upper lip while a patient in the hospital. He also mentions 3 other cases that are referred to by Willis, each from a rare or anaplastic form of cancer of the bladder. Nine hundred two epithelial tumors of the urinary bladder were registered with the American Urological Association in 1934. Two cases were listed with skin metastasis. Liljencrantz, in the Cancer Handbook of the Stanford University Press, states that of 1000 patients dead of carcinomas and autopsied at the Stanford University Hospital, 36 primary bladder carcinomas were found. Only one was found to have skin metastasis. Higgins and Hausfeld report 2 additional cases and make a plea for report of such cases for future evaluation of treatment of carcinoma of the bladder. Our case represents the twelfth reported.

CASE REPORT

E. F. H., a white man aged 71 years, was first seen in the office April 9, 1949, with the chief complaints of frequency and urgent, painful urination, interval urinations every 5 minutes day and night. His urine was grossly bloody. He had a net weight loss of 40 pounds in 3 months. Rectal examination revealed an essentially normal prostate with a grade I hypertrophy. Blood pressure was 120/65.

He was admitted to the hospital for further studies and palliative relief. Cystoscopy under spinal anesthesia showed a bladder capacity of less than 2 ounces, with an extensive infiltrating carcinoma of the bladder. Excretory urograms demonstrated a moderate left hydronephrosis with hydro-ureter and a nonfunctioning right kidney. These films did not demonstrate bony metastasis. Biopsy of the bladder wall at the time of cystoscopy showed a grade 3 undifferentiated infiltrating carcinoma of the bladder. Following supportive therapy for severe hypoproteinemia and severe secondary anemia, the patient was prepared for urinary diversion. On May 10, 1949, cutaneous ureterostomies were performed through bilateral McBurney type muscle-splitting incisions. Just lateral to the line of the left skin incision and in the subcutaneous tissue was a nodule measuring 1.5 by 1.3 by 0.7 cm. which was removed for microscopic study. This proved to be metastatic carcinoma from the bladder (fig. 1). The post-

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Read at annual meeting, American Asociation of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

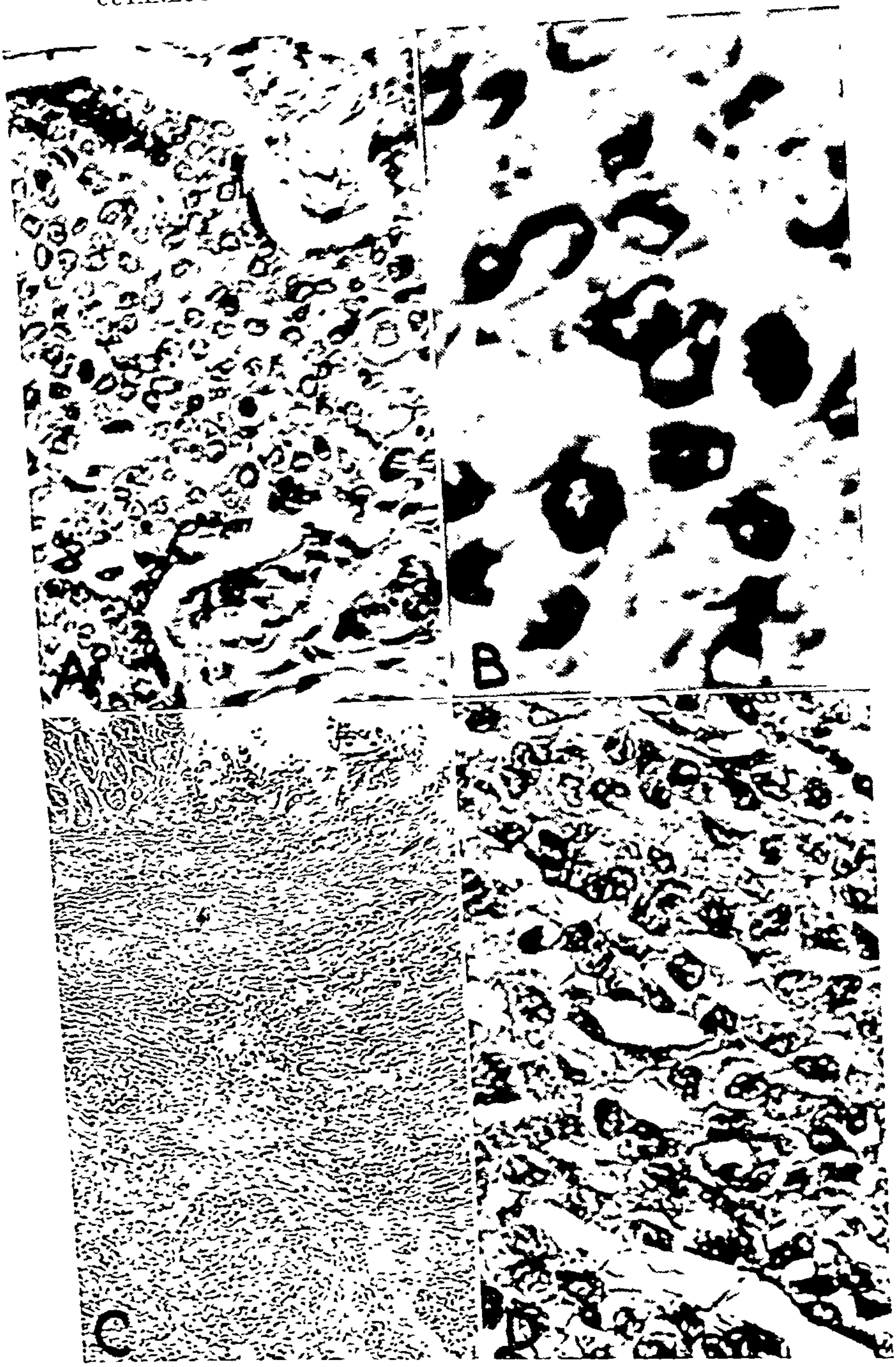

Fig. 1. C, low power section demonstrating infiltration of tumor tissue in subcutaneous layer with both normal and ulcerated epithelium alone. A, B and D, higher magnifications of areas of tumor cells.

operative course was relatively smooth and the patient demonstrated remarkable symptomatic relief. He improved so much that cystectomy seemed justified. This was performed June 30, 1949. Sections of the removed specimen showed invasion of the prostate and seminal vesicles. His immediate postoperative course was considered to be normal, but 4 weeks later he began to go downhill and he died September 8, 1949, five months from the date of his first visit. Autopsy was not obtained.

CONCLUSIONS

A case report is presented which demonstrated a cutaneous metastasis on the anterior abdominal wall originating from a carcinoma of the urinary bladder.

This metastasis could not have been precipitated by surgery as no surgery had been performed prior to its removal.

It is believed that this finding is not so rare as a review of the literature indicates, but evidence is lacking. This represents the twelfth case reported.

The early demise of our patient emphasizes previous observations that once cutaneous metastasis from carcinoma has occurred, the prognosis is hopeless and death may be predicted in 4 to 6 months.

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REFERENCES

ATKINSON, R. C.: Skin metastasis from bladder tumors. J. Urol., **48**: 350-356, 1942.

COMMITTEE ON CARCINOMA REGISTRY: Cancer of the bladder. A study based on 902 epithelial tumors of the bladder in the Carcinoma Registry of the American Urological Association. J. Urol., **31**: 423-472, 1934.

HIGGINS, C. C. AND HAUSFELD, K. F.: Cutaneous metastasis from carcinoma of the urinary bladder; report of two cases. J. Urol., **59**: 879-886, 1948.

KRETSCHMER, H. L.: Carcinoma of bladder with bone metastasis. Surg., Gynec. & Obst., **34**: 241-246, 1922.

LILJENCRANTZ, E.: Cancer Handbook. Stanford University Press, 1938.

McDONALD, J. H., HECKEL, N. J. AND KRETSCHMER, H. L.: Cutaneous metastasis secondary to carcinoma of the urinary bladder. Arch. Dermat. & Syph., **61**: 276, 1950.

ROLNICK, H. C. AND O'NEILL, C. P.: Skin metastasis in carcinoma of bladder. Arch. Dermat. & Syph., **26**: 882-885, 1932.

WILLIS, R. A.: The Spread of Tumors in the Human Body. London: J. A. Churchill & Co., 1934.

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SALPINGOVAGINAL FISTULA: REPORT OF CASE

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Profuse drainage from the vagina which follows hysterectomy is usually due to vesicovaginal or ureterovaginal fistula, occurring as a result of accidental injury to the bladder or to one or both ureters. The resulting escape of urine may be total in the case of vesicovaginal fistula so that no urine collects in the bladder and the patient is never able to urinate in a normal manner. If the injury is to only one ureter the escape of urine is usually constant but the patient voids urine at regular intervals from the intact bladder providing the opposite kidney is present.

Recently we have seen a patient who presented a very interesting problem of profuse constant drainage from the vagina which did not result from injury of either the ureters or the bladder.

CASE REPORT

A white married woman, aged 53 years, admitted October 25, 1949, stated that she had undergone vaginal hysterectomy August 17, 1949, elsewhere. The uterus was said to contain multiple fibroids. Three days postoperatively she began to dribble fluid from the vagina, presumably urine, and this continued in spite of numerous catheterizations of the left ureter, which was thought to be the site of injury which had occurred during the operation. The surgeon made a diagnosis of injury to the left ureter because he found it difficult to introduce a catheter into the ureter. Pyelograms did not demonstrate a fistula. In spite of the use of an inlying catheter in the ureter for the greater part of two months, the drainage continued.

Examination showed a rather apprehensive and somewhat hypersensitive individual, but no physical abnormality could be demonstrated other than profuse, watery vaginal discharge. An excretory urogram showed both kidneys functioning normally and there was no evidence of dilatation of the calyces, pelves or ureters. Cystoscopic examination with the patient under anesthesia revealed a normal bladder; a catheter could be passed up the left ureter without the slightest difficulty. Vaginal examination with a speculum disclosed a small opening high in the left vault from which watery fluid drained. A catheter could be passed into this, with some difficulty, for approximately 3 cm. The catheter in the ureter and the one in the opening in the vaginal vault were injected with medium; they apparently demonstrated a sinus lying adjacent to the ureter, but no clear-cut communication with the ureter could be seen (fig. 1,A). A tentative diagnosis of ureterovaginal fistula was made but since there seemed to be some hope of spontaneous closure, surgical treatment was postponed.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

The patient was dismissed on October 29, 1949, with instructions to report to her home physician for a number of weeks' observation.

She returned to the clinic on December 29, 1949, stating that the dribbling had continued unchanged. The normal size of the ureter as seen by excretory urography seemed to exclude the presence of a ureterovaginal fistula because in our experience, increase in the caliber of the ureter above the site of a fistula is always found. Further study was made the next day. The bladder was again examined very carefully and there was no sign of a vesicovaginal fistula. A large catheter could be passed up the left ureter without the slightest difficulty. The vagina was then examined with a speculum and the minute opening in the left vault was still present and from it watery fluid was observed to drain. A small ureteral catheter was passed into the opening and no obstruction was encountered, so approximately 20 cm. of the catheter was passed into it. The bladder was then filled with water colored with indigo carmine; none of this appeared in the vagina, nor did it drain from the catheter. A roentgenogram was then made after injecting opaque medium into the small ureteral catheter (fig. 1,*B*). This demonstrated a collection of medium in the cul-de-sac and outlined the irregular spaces between the loops of bowel which were lying in the cul-de-sac. The diagnosis of left salpingovaginal fistula was made. We believed that the profuse drainage of watery fluid was peritoneal fluid which escaped through the patent fallopian tube.

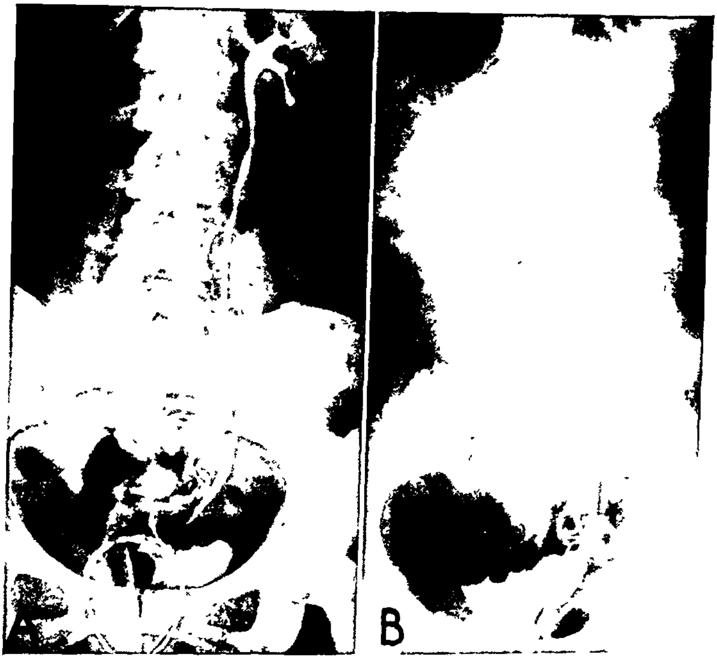

FIG. 1. *A*, left retrograde pyelogram showing normal-sized ureter. Catheter in sinus tract, also injected, shows extravasated medium adjacent to ureter but not communicating with it. *B*, large catheter is in the ureter. A small catheter is coiled in left side of cul-de-sac. Medium which has been injected outlines typical bowel pattern.

Operation was performed on January 4, 1950. When the abdomen was opened the No. 4 ureteral catheter could be seen coming into the peritoneal cavity through the fimbriated end of the fallopian tube (fig. 2). This tube, ovary and sigmoid were all matted together. The sigmoid was separated from the mass, and the ovarian pedicle and left tube were removed close to the vaginal wall. The area was peritonized. The cul-de-sac was otherwise normal. The abdomen was closed with chromic catgut sutures.

The patient's convalescence was uneventful. At the time of dismissal there was a minimal amount of vaginal discharge. A letter received recently stated that she is still troubled at times with urgency of urination which on occasions is so marked that she wears a vaginal pad, but she also informed us that the leakage is much less than she noted preoperatively. She has been advised to return for further examination but up to this time has not complied.

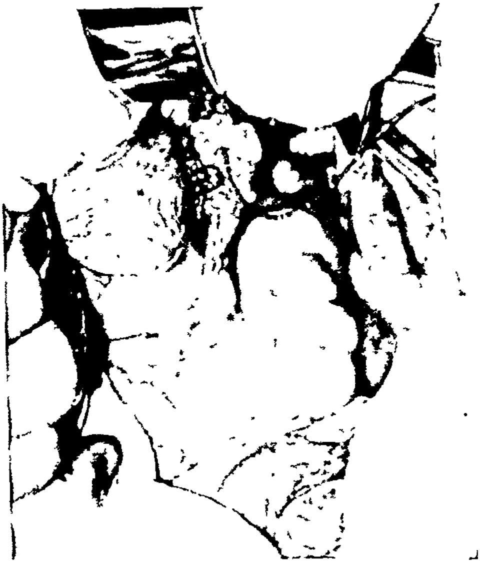

FIG. 2. At time of operation, catheter was seen coming into peritoneal cavity through fimbriated end of fallopian tube.

COMMENT

Prolapse of the fallopian tube has been reported by a number of authors, according to McElin and Ferris who reported 2 cases of their own and also referred to 10 others which had been reported in the literature. This condition, however, is unlike that encountered in our case because very profuse drainage persisting over a period of months was not described as occurring commonly with prolapse of the tube. Rather the fimbriated end of the tube was responsible for vaginal bleeding and bloody discharge. The unusual appearance was suggestive of neoplasm in some cases.

The lack of ureterectasis which is always seen when ureteral injury has occurred and has resulted in fistula formation, was the diagnostic point which led us to study this condition further and enabled us to arrive at the proper diagnosis.

REFERENCE

McELIN, T. W., AND FERRIS, D. O.: Prolapsed fallopian tube as a complication of vaginal hysterectomy: Report of 2 cases. Proc. Staff. Meet., Mayo Clin., 24: 447–452, 1949.

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TECHNIQUE OF RETROPUBIC PROSTATECTOMY

EDGAR BURNS

From the Department of Urology, Ochsner Clinic and the Division of Urology, Tulane University of Louisiana, School of Medicine, New Orleans, La.

The original technique of retropubic prostatectomy and its various modifications have all been described in the medical literature. The complications arising in some cases and the poor end results obtained in others are not necessarily the fault of the method, but might be attributed in some cases to its improper application. The retropubic operation, like any other surgical procedure, must be correctly performed if a good result is to be obtained. Proper selection of cases, together with careful handling of the various structures involved in performing the operation, will largely prevent many of the criticisms now directed toward this method of treatment of vesical neck obstruction. After adequate trial with retropubic prostatectomy, we are now using the method for removal of large, benign prostatic hypertrophies and a modification of it for obstruction at the vesical neck in children. Our discussion will be confined to a description of the technical procedures for removal of obstructions produced by these two lesions.

LARGE BENIGN PROSTATIC HYPERTROPHY

The important structures involved in the retropubic operation for benign prostatic hypertrophy are the precapsular veins, true and false prostatic capsules, the adenoma and the prostatic arteries. Errors in handling these structures account largely for the difficulties encountered in performing the operation.

As a result of a wide experience with more than a thousand cases of retropubic prostatectomy, Millin has made technical modifications which appear to offer more ease of performance, fewer postoperative complications and better end results than any other suggested changes in his technique. We believe that for best results his present technique should be carefully studied and closely followed. There are a number of important points, which might be desirable to discuss here.

1. Elevation of the pelvis suggested by Rolnick (fig. 1, *A*) facilitates exposure by bringing the neck of the bladder to a higher level in the pelvis. Adequate space can be provided by a transverse incision (fig. 1, *B*) a fingerbreadth above the symphysis pubis with separation of the recti; this type of incision leaves a strong abdominal wall.

2. It is important to dispose of the precapsular veins gently but adequately. The size and number of these veins vary in different individuals. The smaller ones may be handled by clamp and electrocoagulation but the larger ones should be ligated. Because of their thin walls the ligatures will frequently cut through. To avoid this the needle should be passed beneath the vein and it

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should include some of the superficial layers of the fibrous capsule, and the ligature should be tied over a small fat pad, as indicated in figure 1, *C*.

3. A small gauze pack introduced in the lateral fossa will enlarge the exposure in most cases. If it is used it should be inserted lightly and removed before enucleation is begun. Placing the packs too deeply and allowing them to remain during enucleation may possibly account for obturator neuritis.

4. Two traction sutures are inserted into the prostatic capsules, one 0.5 cm. and the other 1.5 cm. below the vesical neck and the ends left long. These are used for traction of the capsule during enucleation and for supplementary closure after enucleation has been completed. A transverse incision is made in the capsule starting on the right lobe and extending across half way between the two traction sutures onto the left lobe or a centimeter below the vesical neck (fig. 1, *C*). The length of this incision will vary according to the size of the prostate and should be long enough to permit delivery of the prostate without laceration of the capsule. The importance of making this incision deep enough to go through the true and false capsules and even into the adenoma should be emphasized (fig. 2, *A*). An incision of insufficient depth may lead to an attempt to start the enucleation between the true and false capsules and result in troublesome bleeding. Not infrequently an artery can be seen spurting from the center of the upper and lower flaps. This should be controlled by suture or coagulation. The venous oozing from the cut margins of the capsular flaps is usually unimportant but if necessary it may be controlled by T-clamps until the capsule is sutured.

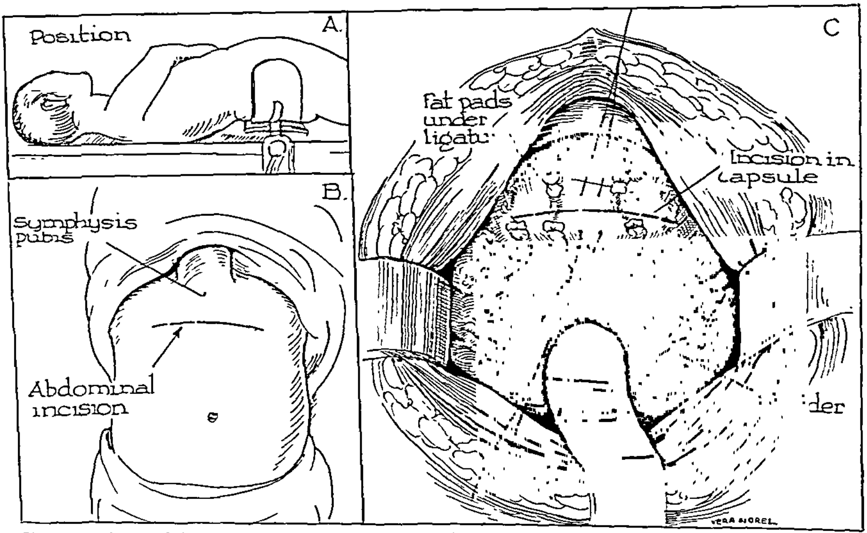

FIG. 1. *A*, position of patient for retropubic prostatectomy. (After Rolnick.) *B*, transverse incision is made a fingerbreath above symphysis pubis. *C*, veins ligated over small fat pad to avoid ligatures cutting through thin walls.

5. The apex of each lateral lobe is then separated from the capsule by means of curved scissors (fig. 2, *B*, *C*) and the prostatic urethra is severed at the apex

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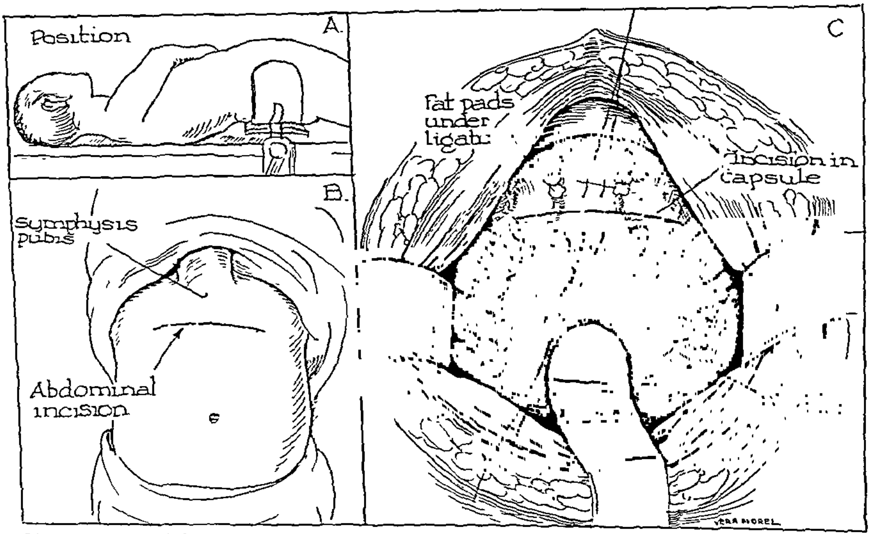


FIG. 1. *A*, position of patient for retropubic prostatectomy. (After Rolnick.) *B*, transverse incision is made a fingerbreath above symphysis pubis. *C*, veins ligated over small fat pad to avoid ligatures cutting through thin walls.

5. The apex of each lateral lobe is then separated from the capsule by means of curved scissors (fig. 2, *B*, *C*) and the prostatic urethra is severed at the apex

(fig. 2, *D*). It is important to sever the urethra partially or completely during this maneuver in order to prevent undue traction on the membranous urethra during the attempt to free the apex of the adenoma. This may lead to temporary or even permanent incontinence. This point was not strictly observed in one of our cases and traction was put on the urethra in freeing the apex before the error was recognized. The patient had total incontinence for a few days and partial incontinence for 3 weeks.

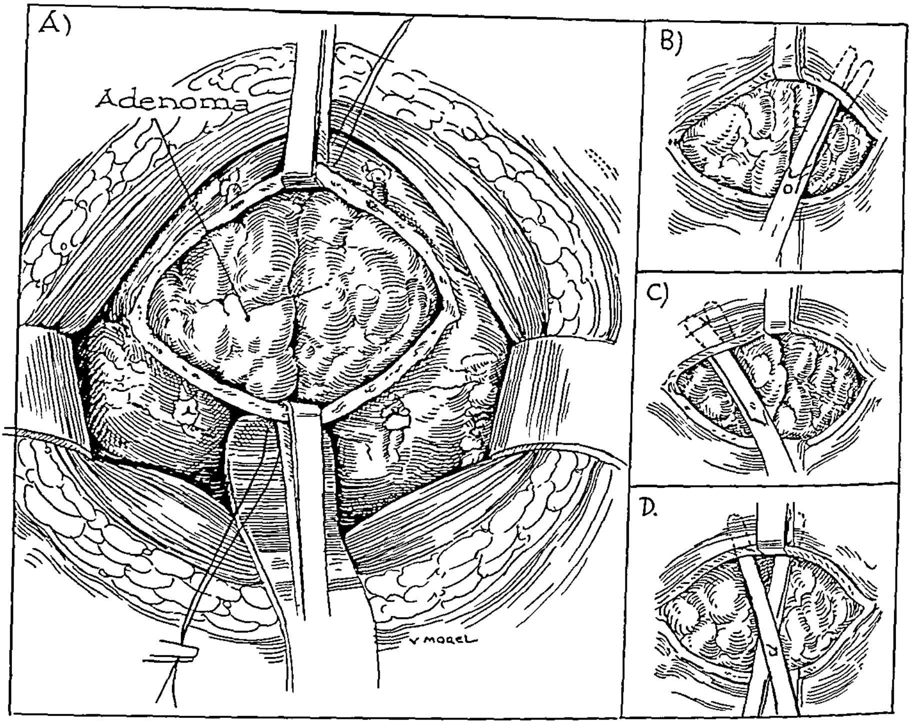
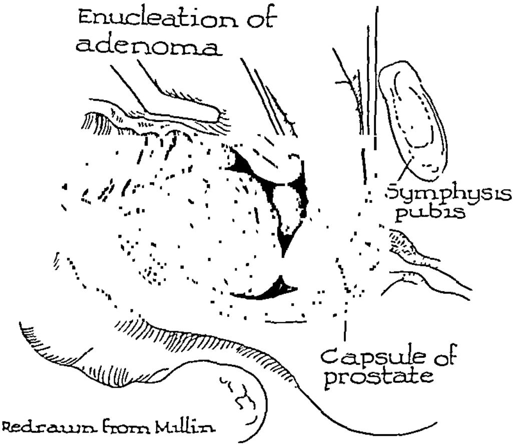


FIG. 2. *A*, incision in capsule visualizing the adenoma. *B*, *C*, apex of each lobe is separated from capsule by means of curved scissors. *D*, prostatic urethra is severed at apex.



Redrawn from Millin

FIG. 3. Establishing correct line of cleavage makes enucleation easier with normal amount of trauma.

6. Gentleness is of utmost importance in performance of the enucleation (fig. 3). A traumatizing procedure may tear the capsule, resulting in unnecessary bleeding, which may be difficult to control, and this may predispose to drainage of urine through the wound and other postoperative complications.

7. Adequate hemostasis is as important in this as in other types of prostatic surgery. The prostatic arteries can be easily visualized and ligated with transfixion sutures (fig. 4, *B*). Venous oozing is rarely of clinical importance and usually stops when the prostatic capsule contracts. We have not found it necessary to use a hemostatic bag or pack hemostatic agents into the prostatic cavity to control bleeding.

8. After hemostasis is complete, the prostatic cavity should be carefully inspected for small adenomas or tags, all of which should be removed, and the cavity left perfectly smooth.

9. In the majority of cases the posterior lip of the vesical neck is elevated and a generous wedge should be removed from this area (fig. 4, *A*). Bleeding that results from removal of this wedge should be controlled by spraying with a fulgurating current or by sutures.

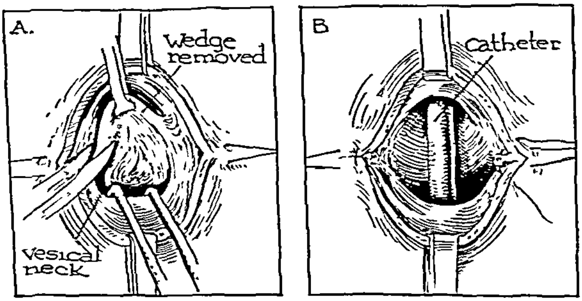


FIG. 4. *A*, generous wedge is removed from posterior lip of vesical neck. *B*, ligation of prostatic arteries with transfixion sutures and placing of retention catheter in bladder.

10. The retention catheter should not be too large—in the majority of cases, not larger than a 20 or 22F. Larger catheters are not only uncomfortable but may predispose to the development of strictures. The catheter is guided through the vesical neck to a proper position in the bladder. If a Foley type of catheter is used, the bag should be sufficiently distended to prevent slipping down into the prostatic urethra, in which case drainage is inadequate and urine will leak through the wound.

11. The capsule is closed by a continuous layer of No. 1 chromic catgut sutures (fig. 5). The traction sutures are then tied for further support of the closure. We have discontinued using the boomerang needle to suture the capsule and now favor the small, full curved needle, which appears less traumatic. The capsular suture should be hemostatic as well as water tight. At this point in the operation the space of Retzius should be perfectly dry. If any oozing exists, this may be controlled by a light pack, which is brought out through the wound and removed at the end of 24 to 48 hours. The abdominal wound is closed in layers and the Penrose drain is left in the space of Retzius for 4 or 5 days or until the dressing has remained dry. Particular care is exercised throughout the operation

to avoid trauma to the periosteum. An injured periosteum exposed to an accumulation of infected urine in the space of Retzius is considered to be a chief predisposing factor to osteitis pubis. For this reason, we believe that the space of Retzius should be drained for a longer period than is practiced at the present time. The patient may be out of bed at the end of 24 to 48 hours and if there is no leakage of urine the catheter may be removed at the end of 4 or 5 days. Stones in the bladder or lower ureter may be removed at the same time retropubic prostatectomy is performed without complicating or prolonging the postoperative period.

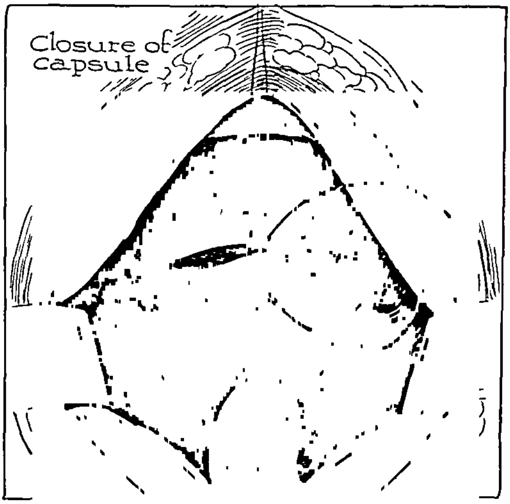


Fig. 5. Closure of capsule by continuous layer of No. 1 chromic catgut sutures

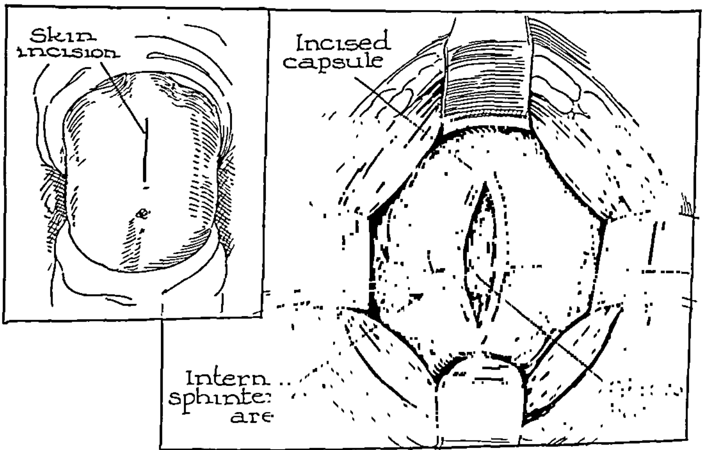


Fig. 6. Modified retropubic prostatectomy for removal of vesical neck obstruction in children. Incision made just above internal sphincter and extended through vesical neck and distally as far as necessary to expose prostatic urethra. Inset shows cutaneous incision.

VESICAL NECK OBSTRUCTION IN CHILDREN

We have utilized a modification of the retropubic operation for removal of vesical neck obstruction in children. A longitudinal abdominal incision is extended from the upper margin of the symphysis pubis upward for a distance of 5 to 7.5 cm. (fig. 6). The vesical neck is exposed; an incision is made just above the internal sphincter and extended through the vesical neck and distally as far

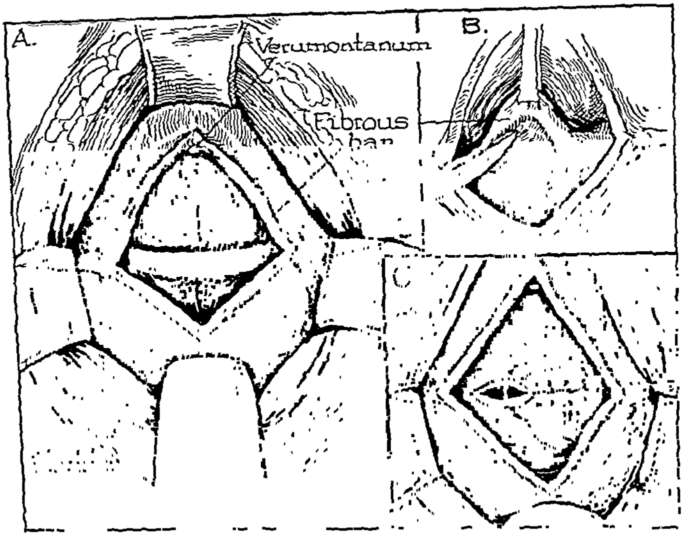


FIG. 7. *A*, exposure of entire prostatic urethra to full view. *B*, excision of obstruction. *C*, closure of defect created by removal of obstruction.

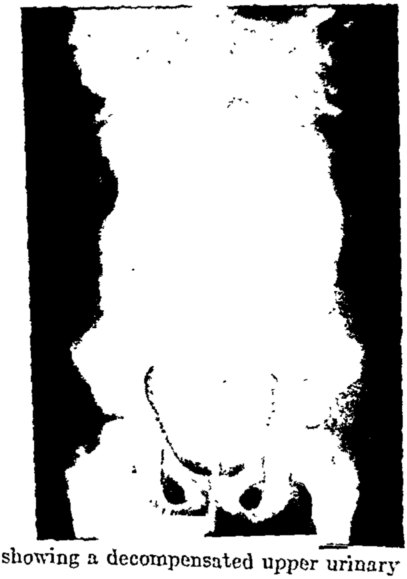


FIG. 8. Cystogram showing a decompensated upper urinary tract requiring suprapubic drainage.

as is necessary to expose the entire prostatic urethra to full view (fig. 7, *A*). It may be carried through the entire length of the prostatic urethra but this is rarely necessary. Congenital bars are excised under vision (fig. 7, *B*) and the raw surface thus created is covered by approximating the cut edges with interrupted sutures. Prostatic valves may be destroyed by electrocoagulation. The loss of blood is usually minimal and bleeding points are dealt with individually. A catheter is inserted through the urethra and the incision in the capsule and bladder is closed with continuous sutures (fig. 7, *C*). This completes hemostasis and leakage of urine rarely occurs. The catheter should be left in until the wound appears healed, usually 7 to 10 days. In those patients whose upper urinary tract shows severe damage a stab wound is made high in the bladder and suprapubic drainage is instituted (fig. 8). This should be continued until the upper urinary tract has had a maximum opportunity to regain its function, usually 6 months or more.

We have used this method in 9 cases with no deaths, no significant post-operative complications and uniformly satisfactory end results. From this brief experience it is our belief that this method may completely replace transurethral resection for removal of vesical neck obstruction in children. Lich and Maurer reported uniformly satisfactory results in 5 cases in which this method was used. There are probably others which have not yet been reported.

SUMMARY

We prefer Millin's technique of retropubic prostatectomy for removal of large, benign prostatic hypertrophy. The details of this technique are described and illustrated.

A modification of the retropubic operation, which is described in detail and illustrated, has been used in 9 cases of vesical neck obstruction in children with no deaths, no significant postoperative complications and satisfactory end results. It is our opinion that this method may entirely supplant transurethral resection for removal of obstructions at the vesical neck in children.

REFERENCES

Lich, R., Jr. and Maurer, J. E.: The surgical relief of vesical neck obstruction in children. South. Surg., **16:** 127–131, 1950.
Millin, T.: Retropubic Urinary Surgery. Edinburgh: E. & S. Livingstone, Ltd., 1947.
Rolnick, H. C.: Practice of Urology. Philadelphia: J. B. Lippincott Co., 1949.

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INDICATIONS FOR RETROPUBIC PROSTATECTOMY

CARL RUSCHE

The subject of the surgical approach to the prostate is a very trite one. Numerous articles and treatises have been written about it for decades, yet the difficulties of removal of the prostate gland remain.

Mr. Terence Millin's method of extravesical prostatectomy has been received in this country and abroad, with considerable enthusiasm. It is his belief that retropubic prostatectomy is the most universally applicable operation yet devised to eliminate the evils of the obstructing prostate, and that it is suitable for all types of prostatic obstruction.

The experiences of a relatively large number of authors indicate that Millin's retropubic operation is extremely simple, and is attended by few serious complications, with comparatively little mortality provided his operative procedure is carefully employed and good hemostasis is obtained at the time of surgery. The beneficial features are:

1) The operative field is amply exposed so that all stages of the procedure are performed under direct vision.

2) There is no injury to or interference with any vital organ.

3) The urinary bladder is not opened, thus reducing operative shock, avoiding the inconvenience of delayed healing and lessening the chance of a persistent fistula. Almost always the wound heals by primary intention.

4) The adenomatous prostate is completely enucleated and the bladder orifice is well exposed so that a subtrigonal lobe may be readily removed.

5) The mortality rate is low.

As a result of my experiences, I have found that the retropubic operation is comparatively free from risks and complications encountered in the removal of the prostate by other approaches; however, some of the complications include the following: 1) primary hemorrhage, 2) secondary hemorrhage with pericystitis and suppuration, 3) postoperative urinary fistula, 4) osteitis pubis, and 5) impotence.

Generally speaking, I believe the transurethral approach is the method of choice in the small prostate, the fibrous bar at the bladder neck, or for palliation in prostatic cancer. Perineal prostatectomy is usually preferred in cases of early prostatic carcinoma, prostatic calculosis and in the poor risk patient with marked renal insufficiency.

I have only performed radical retropubic prostatectomy on two occasions, and although I tried to follow the technique described by Millin as closely as possible, I found it extremely difficult to suture the vesical neck to the urethral stump. In order to draw the bladder neck to the urethra, it was necessary for me to rely on tension with a Foley catheter for approximation. The postoperative course of one patient was entirely without complications; the other developed symptoms

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associated with osteitis pubis. This experience has deterred me, temporarily at least, from further use of the method of radical retropubic prostatectomy.

Millin has devised a unique surgical procedure for the removal of the prostate gland, and it has proved to be a valuable addition to our armamentarium in the treatment of prostatism. However, I have had no occasion to change my conviction that the method of prostatectomy should be adopted to meet the needs of the patient, not the patient forced to conform to the limited skill of the surgeon.

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RETROPUBIC PROSTATECTOMY: RESULTS AND COMPLICATIONS

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In 1945 Millin first utilized the extravesical retropubic approach for prostatectomy and the same year described his technique and reported his experience in 20 cases. Since then a sufficient number of retropubic prostatectomies have been performed in this country and abroad to indicate that the procedure has established itself as one of merit and one which will undoubtedly be used extensively, although hardly sufficient time has elapsed to permit a true evaluation of the late results of the operation.

The material for this discussion of results and complications comprises 116 cases in which more than a year has elapsed since the operation. Sixty-seven of this group were from private practice and forty-nine, largely charity cases, were from the urologic service of the John Gaston Hospital, College of Medicine, University of Tennessee, including those operated upon by my associates and the resident staff. Of the entire group it has been possible to tabulate the results in 60 of the private cases and in 27 from the charity service, a total of 87. A recent survey revealed that 14 patients could not be traced and that 15 have expired from various causes since they were dismissed from the hospital.

In arriving at the merits of any surgical procedure due consideration must be given the immediate and remote functional results, the incidence of complications, morbidity and the mortality rate. A critical review has been made of the clinical records of these patients and data pertaining to late results have been obtained both through personal observation and from the submission of a questionnaire. While the latter method of obtaining information is not altogether satisfactory, it provides a means of securing data which otherwise would not have been available as many of these patients live at distant points and found it impractical to return for examination. The questionnaire sought specific information regarding the state of the general health, gain or loss of weight, sexual power, urinary difficulty, bladder function, urinary control, nocturia, hematuria, pyuria, pyelonephritis, pain or discomfort in the region of the pelvis or thighs and there was a request for any general remarks the patient might care to include.

Inasmuch as results and complications may be directly related to the choice of cases and the considered indications for an operation, it may be stated that this series is limited to those in which the large size of the gland was such that enucleation seemed preferable to removal in small segments transurethrally. The rule has been adopted that if the necessity of removing 50 or more grams of tissue is anticipated, prostatectomy by some method of enucleation is preferable to transurethral resection. In our experience about 75 per cent of cases of benign

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hyperplasia of the prostate, associated with obstructive symptoms of such degree as to warrant surgical interference, have been dealt with very satisfactorily by transurethral resection and about 25 per cent have been subjected to open operation and enucleation of the adenofibromatous mass. There has not been included in this series any instances of known carcinoma of the prostate although in six of the cases which were considered clinically of benign character, the pathologic diagnosis was adenocarcinoma. It might be stated further that early in our experience with retropubic prostatectomy a very favorable impression was gained of the operation which prompted us to adopt this procedure in preference to suprapubic prostatectomy and as a result very few glands have been enucleated suprapubically, either by the one- or two-stage methods since we performed the first retropubic prostatectomy three years ago. The immediate and late results of the operation have been observed with the keenest interest and it may be frankly stated at the present time that although some serious complications have occurred, they have been relatively infrequent. Disadvantages are so far outweighed in the rank and file of cases by such advantages as the marvelously short and smooth convalescence, excellent functional results and remarkably low mortality rate, that we have felt justified in continuing to use the procedure.

REVIEW OF CASES

Age. The age of the patients in this series varied from 50 to 86 years and the average age was 69.5 years. Eighty-three of the patients were between 60 and 79 years and there were ten 80 years or more of age. Most of the infirmities usually seen in geriatic practice were encountered and the usual safeguards pertaining to the preliminary clinical study, preparatory treatment and postoperative care were routinely observed.

Size of gland. An estimate of the size of the obstructing prostate was obtained through a combination of the digital examination and pneumocystography. Cystoscopy was employed in very few of the cases although it undoubtedly would have provided a more accurate estimate of the size of the gland. It has been our feeling, however, that preliminary cystoscopy, in the presence of a large obstructing prostate, incurs a definite and unnecessary risk and should be avoided whenever reasonably possible unless some unusual and important indication presents itself. In this group the average weight of the glands removed was 75.6 gm. The largest gland weighed 250 gm. and there were 12 which weighed 30 gm. or less. No doubt, all the latter could have been dealt with very satisfactorily by transurethral resection but their size had been overestimated in the preliminary clinical investigation.

Technique. In all of the cases a low transverse incision has been used with division of the sheath of the recti, separation of the muscles in the midline and their gentle retraction. In the first 36 retropubic prostatectomies the larger veins comprising the plexus of Santorini were grasped with hemostats and electrocoagulated. In the remainder of the group the prostatic capsule has been incised between hemostatic sutures employing an ordinary scalpel, whereas formerly the capsule was divided with the electric scalpel. These details are mentioned because the impression has been gained that certain late complications may possibly be related to such seemingly minor technicalities. All in all, the technique of the operation as described by Millin has been followed fairly closely including the greatest care in the preliminary toilet of the bladder, careful suturing of the prostatic capsule with the view of attaining a watertight closure, the scrupulous avoidance of trauma to the pubic bone or its periosteum, the excision of a v-shaped segment from the posterior margin of the vesical neck, good visualization of the prostatic cavity with extreme care regarding hemostasis, the employment of the sulfonamides and antibiotics, the early removal of the postoperative inlying catheter, usually by the third day, and, lastly, early ambulation.

Immediate results. Inasmuch as this discussion is concerned primarily with late results and complications, only brief mention will be made of the immediate postoperative course. As a rule, these patients are remarkably free from shock and are definitely more comfortable than is observed when the bladder has been opened suprapubically. The degree of postoperative hematuria compares favorably with that seen in the usual transurethral resection when good hemostasis has been attained. In most cases by the third day drainage is usually clear or only slightly discolored and the catheter is removed, after which the patient is allowed to be up and about. In the immediate postoperative period there were 9 instances of infection involving the incision, none of which was serious, and the remainder healed per primam. In the group of private patients, the period of postoperative hospitalization varied from 7 to 31 days, averaging 10.6 days.

General health. Definite improvement in the general health was reported by 77 patients (88.5 per cent) and no change in general health by 10 (11.5 per cent).

Weight. Forty-nine patients (56.3 per cent) reported gain in weight and in one instance this amounted to 43 pounds within 17 months following operation on a diabetic 75 years of age. Thirty-one (35.6 per cent) reported their weight unchanged, in 4 (4.5 per cent) there had been loss of weight and in 3 there was no report.

Sexual power. Data regarding sexual power are of interest inasmuch as variable effects have been noted, depending upon the approach adopted in prostatectomy. It is generally known that sexual power is usually diminished following perineal prostatectomy and this has been listed by numerous writers as one of the objections to the procedure. In this group sexual power was reported definitely improved by 11 patients (12.6 per cent), was unchanged in 61 (70.1 per cent) and diminished in 5 (5.7 per cent). There is reason to believe that deleterious effects in this regard are less following retropubic prostatectomy than in any other surgical approach to the prostate gland.

Bladder function. Bladder function was reported satisfactory by 86 patients (98.8 per cent) and unsatisfactory by 1 (1.2 per cent). In this case there was a heavily infected vesical diverticulum with nocturia of 3 to 4 times in a patient 88 years of age who survived a secondary retropubic prostatectomy fifteen months. Eight-two patients (94.2 per cent) reported no urinary difficulty; 5 (5.8 per cent) reported recurrence of urinary difficulty, in 3 of whom it was of mild degree and of no consequence; in 1 there was definite evidence of carcinoma of the prostate with metastases 13 months postoperatively and in another case there was moderate contracture of the vesical neck but no residual urine twenty months following operation.

Urinary control. Urinary control was reported normal by 76 of the patients (87.4 per cent). Slight terminal dribbling was reported by 11 (12.6 per cent). There was not one instance of urinary incontinence.

Nocturia. The degree of nocturia may be considered an index to the functional result in a given case. By referring to table 1 it is noted that 17 patients (19.4 per cent) reported no nocturia and in 78 (89.6 per cent) there was nocturia of only none to three times.

Other data. The urine was reported clear by 73 patients (84 per cent) and cloudy in variable degrees, usually mild, in fourteen (16 per cent). Pyelonephritis as a late complication did not occur, although 4 patients reported fever of moderate degree, one from epididymitis 18 months postoperatively. In two others fever was associated with osteitis pubis and in another case it was caused by a stitch abscess one year following operation.

TABLE 1. *Incidence of nocturia following retropubic prostatectomy*

None...	17	(19.4%)
0 to 1..	20	(22.7%)
1 to 2	27	(31.2%)
2 to 3	14	(16.7%)
3 to 4	3	(3.5%)
4 or more	6	(6.8%)

COMPLICATIONS

Epididymitis. Formerly vas ligation or partial vasectomy was performed routinely in the surgical treatment of prostatic obstruction. With the advent of modern chemotherapy and the antibiotics, the impression was gained that their use routinely in the preliminary and immediate postoperative periods would prevent epididymitis and the practice of ligating or sectioning the vas was abandoned. In the group under discussion there was no interference with the vas in 59 cases, among which epididymitis occurred in 6. None of these progressed to suppuration, however, nor did any require epididymotomy. In the group subjected to ligation or vasectomy there were 2 instances of acute epididymitis. At present, reliance again is placed upon chemotherapy and the antibiotics for the prevention of epididymitis.

Hemorrhage. Late secondary vesical hemorrhage occurred in 7 cases (8 per cent), in 3 of which it would be considered severe, requiring one or more blood transfusions. In three there was gross hematuria of lesser degree, in one on the seventh postoperative day and in two others on the fourteenth and thirty-fifth postoperative days, respectively, but of a degree easily controlled by re-insertion of a Foley catheter and clearing the bladder of clots.

Persistent or recurrent urinary difficulty. Following the enucleation of a large benign prostate by any standard technique, the persistence or return of urinary difficulty is always a matter of concern. It may be due to vesical atony, contracture of the vesical neck, a stricture of the urethral meatus, adenomatous remnants in the prostatic fossa, or to recurring obstruction from carcinoma.

Early recurrent obstruction occurred 5 times in Millin's first 75 cases (6.6 per cent). Since he adopted almost routinely the excision of a wedge from the posterior margin of the vesical neck, the complication occurred in only 3 cases out of 675 (.44 per cent). Wilhelm and Freed reported stricture of the neck of the bladder in 9 cases out of 33 retropubic prostatectomies. In this series of 116 there were 3 instances (2.5 per cent) of vesical neck contracture. Two of these occurred in spite of the fact that a v-shaped segment had been excised from the posterior margin of the vesical neck. In one this had not been done. Recurrent urinary difficulty reported by two other patients was found to be due to a stricture of the urethral meatus which was relieved by meatotomy 1 month and 5 months, respectively, following operation. It is of interest to note that a resectoscope, an instrument so often blamed for meatal stricture, had not been used in either of these patients. One of them, however, had worn a 24F Foley catheter for a period of 5 days. Five months later the meatus would admit only a filiform bougie. Another patient experienced a return of urinary difficulty 13 months following operation when an examination revealed definite evidence of carcinoma of the prostate with metastases. In another case in which a greatly overdistended bladder had been drained of 4 liters of urine at the original catheterization, urinary difficulty persisted in spite of a primary retropubic prostatectomy. Eight days following operation there was 660 cc of residual urine due to vesical atony, for which a transurethral resection of the vesical neck was performed with the hope that it would enable him to empty the bladder more completely. At the time of his dismissal 28 days following operation, there was still 330 cc of residual urine. This patient reported, however, 1 year later that bladder function was satisfactory, there was no urinary difficulty and he was highly pleased with the functional result. True vesical neck contracture having occurred in only 3 instances of 116, compares favorably with the incidence of this complication following any other type of prostatectomy. Shivers and Groom, in a review of a large group of collected cases in which suprapubic prostatectomy was performed, reported urethral stricture occurred in 4.6 per cent. The complication is most common following transurethral resection as reported by these authors, having occurred 453 times in 8,508 collected cases (5.3 per cent).

Urinary fistula. There was not a single instance of persistent urinary fistula in this series. Farman and Lemon reported its occurrence in 4 instances of their collected series of 1,149 cases. Millin states definitely that suprapubic urinary leakage usually means faulty capsular suturing. It occurred in 9 per cent of his first 400 cases. In his last 200 retropubic prostatectomies for benign hyperplasia, there were 9 instances of postoperative urinary leakage (4.5 per cent); there were no cases of persistent urinary fistula. A special effort has been made in this series to effect a watertight closure by employing a double row of chromic catgut No. 1 sutures, the inner one of which is interlocked. We have considered it extremely important to prevent urinary leakage into the retropubic space, primarily in order to avoid urinary extravasation and the usual attendant infection, and, secondarily, with the view of preventing a persistent urinary fistula. In this so far our efforts have been successful.

Osteitis pubis. This distressing late complication is by far the most important one because of the prolonged period of disability engendered by it. In a review of the literature pertaining to osteitis pubis, one is impressed with its increasing incidence in recent years, before the introduction of retropubic prostatectomy. Undoubtedly, the complication has been referred to under several different terms among which might be mentioned periostitis pubis (Wilhelm and Freed), osteochondritis (Barnes; Pierson), osteoporosis of the pelvic bones (Bruskewitz and Ewell), chondritis of the symphysis (Lich, Grant and Maurer), and obturator neuritis. Beer in 1924 is credited with the first report of the disease and Rosenberg and Vest in 1948 found 48 reported cases in the literature, 45 in men and 3 in women. There were 42 instances following suprapubic prostatectomy and one each following perineal prostatectomy, symphysiotomy and delivery with vaginal fistula, infected herniorrhaphy and cystostomy, occupational trauma to the lower abdomen and acute pyelonephritis. McGinn in 1949 reported a fourth case in a woman following ureterolithotomy.

The exact etiology and pathogenesis of osteitis pubis have remained somewhat obscure. Most authors stress the importance of avoiding traumatizing the periosteum of the pubic bone such as might be incurred by the prick of a needle, injury from retractors, excessive heat from electrosurgery, or too vigorous retraction of the recti muscles. Millin in 1949 reported having experienced the complication 6 times in 757 retropubic prostatectomies; in 3 of these it was of a severe degree. His impression of the possible relationship of the etiology to the use of the sulfonamides and antibiotics is of interest in that these agents may induce "prompt healing of the superficial wound with locking up of Pseudomonas pyocyanea and other resistant organisms. Accordingly, we have now abandoned the routine use of penicillin and employ it only when it appears to be definitely indicated." Beach performed a biopsy in 2 cases which revealed changes in the bone indicative of panosteitis. He expressed the belief that it is caused by trauma, septic spill and inadequate drainage with the accumulation of urine or septic material behind the pubis, overspreading the nutrient foramina. Bruskewitz and Ewell reported three cases and were inclined to agree with Wheeler that the condition is an acute atrophy of bone of the Sudeck type.

From a bacteriologic standpoint several organisms have been suspected in osteitis pubis. Abrams, et al., in 1949 reported 5 cases in all of which culture of the urine revealed Pseudomonas aeruginosa. Muschat obtained a positive culture of B. proteus in 1 case and Kleinberg recovered B. coli. In our series aspiration of material from the region of the involved pubic bone in several cases was submitted for culture, all of which remained sterile. Unfortunately, there has been little opportunity to study these cases thoroughly from a pathologic standpoint as, in most cases, the disease runs its course and is regarded by many as self-limited and is seldom fatal.

In the series under discussion, of the 116 retropubic prostatectomies, there were thirteen instances (11.2 per cent) of osteitis pubis, 6 of which might be regarded as severe, 2 of moderate degree and 5 were mild. The onset of symptoms varied from 2 weeks to 5 months postoperatively, averaging 2 months. Moderate pain and tenderness appear in the region of the symphysis, soon followed by a severe discomfort accompanied by muscular cramps effecting the adductor magnus group of muscles in the inner aspect of the thighs. Paroxysmal pain in these regions is precipitated by any effort to move the pelvis or lower extremities and the patient becomes completely disabled, lying quietly as possible in bed in utter fear of any movement involving the lower torso or thighs. As a rule there is no external evidence of an inflammatory process and the early roentgen examination of the region is essentially negative. In 9 of the cases in this series the incision had healed per primam and in 4, there was a minimal degree of infection in the immediate postoperative period. Later on definite changes occur in the roentgen findings including areas of rarefaction of the pubic bones, increased density of the medial margins of the pubic rami and a widening of the symphysis pubis.

Our experience with this complication has been rather remarkable in that 13 cases were encountered among the first 80 cases (16.3 per cent) of retropubic prostatectomies performed. During the past 21 months the operation has been performed in 79 cases without the occurrence of a single instance of osteitis pubis. These cases have been critically reviewed in an effort to discover the responsible factors. It was realized that the incidence of this complication was entirely too high which prompted the following alterations in technique: More gentle retraction of the recti muscles was adopted; the prostatic capsule was incised between hemostatic sutures where formerly the veins comprising the plexus of Santorini were seized with hemostats and electrocoagulated; the use of the electric scalpel for incising the prostatic capsule was abandoned in favor of a sharp knife; an aqueous solution of sulfamylon containing 5,000 units of streptomycin per 100 cc for prophylactic reasons was used locally in the prostatic cavity and the entire incision; an all out effort was made to effect a watertight closure of the prostatic capsule as previously mentioned, employing two rows of sutures instead of one. Every conceivable effort has always been made to avoid traumatizing the pubic bone or its periosteum. The relative importance of any one of the possible factors mentioned cannot be definitely stated. The disappearance of the complication, however, has been a most gratifying experience and a source of encouragement to continue employing retropubic prostatectomy in selected cases.

Treatment has included the widespread use of chemotherapy and the antibiotics with rather indifferent results. Rosenberg and Vest advise immobilization of the involved parts, heat and diathermy for symptomatic relief, drugs such as prostigmine and atropine for relief of muscle spasm, incision and drainage if a pelvic abscess develops and adequate sedation. Vitamin B-1 in massive doses has also been suggested, especially in those cases in which a possible obturator neuritis is in evidence. Goldstein and Rubin in 1947 advocated the use of deep roentgen therapy and, in our experience, this has proved to be the most worthwhile single therapeutic agent, especially if the complication is recognized early and roentgen therapy is initiated promptly. In one of our cases with fully developed symptoms, there was very prompt improvement after 300 roentgen units of therapy and he was able to walk out of the hospital unassisted after 10 days. In several other cases of a more advanced form, there was very definite improvement soon after x-ray treatment was started, whereas they had proved refractory to the other usual measures.

Mortality. There were two hospital deaths in the series (1.7 per cent). A man aged 74 had undergone a considerable degree of urethral trauma from attempts to pass a catheter by his home physician. An emergency suprapubic cystostomy was necessary. His recovery was slow and he was allowed to return home on the eighth postoperative day and was re-admitted for a secondary retropubic prostatectomy 3 months later, having experienced one massive hemorrhage from the bladder in the interval. A gland weighing 140 gm. was removed, following which there was an unusual tendency to bleed and there was low grade fever for a number of days. He received a total of 5 blood transfusions in spite of which he underwent a slow decline. A blood culture revealed Streptococcus faecalis and there was clinical evidence of acute bacterial endocarditis. He expired on the twenty-fourth postoperative day. Necropsy revealed acute bacterial endocarditis and fibropurulent pericarditis. The other death occurred in the case of a man aged 68 on whom a primary retropubic prostatectomy had been performed with removal of a gland weighing 90 gm. The operation was without incident but on the second postoperative day he expired suddenly from coronary occlusion as proved by necropsy. The immediate low mortality rate has been a source of gratification and compares with an over-all mortality rate of 4.1 per cent as reported by Farman and Lemon in their review of 1,149 collected cases. The mortality rate in 757 cases reported by Millin, MacAlister and Kelly was 4.6 per cent.

Fifteen patients of this group have expired from various causes since their dismissal from the hospital, the survival periods varying from 2 months to 28 months. Most of these were unrelated to prostatic obstruction such as: acute leukemia 24 months postoperatively, inoperable carcinoma of the stomach 2 months postoperatively, and several from cardiac disease. When one considers that the average age of the entire group of 116 cases at the time of operation was 69.5 years, the loss of 15 patients from various causes 1 to 3 years following the operation would hardly be considered unexpected since the average age at the time of death was 75.5 years.

SUMMARY

The results and complications are reviewed in a series of 116 retropubic prostatectomies in which more than a year has elapsed since the operation. By means of personal observation and the submission of a questionnaire, inquiry was especially made regarding general health, weight, sexual power, urinary difficulty, bladder function, urinary control, nocturia, hematuria, pyuria, pyelonephritis and osteitis pubis.

Such complications as epididymitis, secondary hemorrhage, persistent or recurrent urinary difficulty, urinary fistula and osteitis pubis are discussed along with a report of their incidence in the series. There were two hospital deaths, indicative of a mortality rate of 1.7 per cent. Fifteen patients, whose average

age was 75.5 years, expired from various causes from 2 to 28 months following operation.

The impression has been gained that through merit retropubic prostatectomy has earned recognition as a standard procedure for the relief of prostatic obstruction along with the other time-honored approaches of suprapubic, transurethral and perineal prostatectomy.

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REFERENCES

Abrams, M., Sedelezky, I. and Stearns, D. B.: Osteitis pubis. New Eng. J. Med., **240:** 637-641, 1949.

Barnes, F. L.: Osteochondritis of symphysis pubis following prostatectomy. Texas State J. Med., **28:** 601-604, 1933.

Beer, E.: Periostitis of the symphysis and descending rami of pubes following suprapubic operations. Internat. J. Med. & Surg., **37:** 224-225, 1924.

Bruskewitz, H. W. and Ewell, G. H.: Osteoporosis of the pelvic bones (acute bone atrophy of Sudeck). Am. Jour. Surg., **77:** 705-712, 1949.

Farman, F. and Lemon, K. A.: Retropubic prostatectomy log. Urol. & Cutan. Rev., **53:** 584-589, 1949.

Goldstein, A. E. and Rubin, S. W.: Osteitis pubis following suprapubic prostatectomy. Am. J. Surg., **74:** 480-487, 1947.

Kleinberg, S.: Osteitis pubis: with a report of a case in a woman. J. Urol., **48:** 635-641, 1942.

Lich, R., Jr., Grant, O. and Maurer, J. E.: Extravesical prostatectomy: A comparison of retropubic and perineal prostatectomy. J. Urol., **61:** 930-942, 1949.

McGinn, E. J.: Osteitis pubis in a female following ureterolithotomy. Urol. & Cutan. Rev., **53:** 264-267, 1949.

Millin, T.: Retropubic prostatectomy: New extravesical technique: Report of 20 cases, Lancet, **2:** 693-695, 1945.

Millin, T., MacAlister, C. L. O. and Kelly, P. M.: Retropubic prostatectomy: Experiences based on 757 cases. Lancet, **1:** 381-385, 1949.

Muschat, M.: Osteitis pubis following prostatectomy. J. Urol., **54:** 447-458, 1945.

Pierson, E. L., Jr.: Osteochondritis of symphysis pubis. Surg., Gynec. & Obst., **49:** 834-838, 1929.

Rosenberg, M. L. and Vest, S. A.: Osteitis pubis. J. Urol., **60:** 767-775, 1948.

Shivers C. H. deT. and Groom, C. E.: Prolonged morbidity following operation for benign prostatic hyperplasia: A statistical survey. J. Urol., **59:** 893-901, 1948.

Wheeler, W. K.: Periostitis pubes following suprapubic cystostomy. J. Urol., **45:** 467-475, 1941.

Wilhelm, S. F. and Freed, S. Z.: Postoperative stricture and periostitis pubis following retropubic prostatectomy. J. Urol., **62:** 660-662, 1949.

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Such complications as epididymitis, secondary hemorrhage, persistent or recurrent urinary difficulty, urinary fistula and osteitis pubis are discussed along with a report of their incidence in the series. There were two hospital deaths, indicative of a mortality rate of 1.7 per cent. Fifteen patients, whose average occurring in the seminal tract. One of our patients developed a scrotal abscess while on drug therapy, adequate we thought; this required incision and drainage. Culture of the pus from the abscess yielded staphylococci.

The age limits in the series of patients varied from 50 to 86 years with 69.4 years as the average.

The usual complaints were frequency, nocturia, dysuria, hesitancy, strangury and dribbling. Of course, acute retention of urine was the usual presenting symptom. To our surprise, 19 patients of the 105 in this series had frank hematuria upon admission to the hospital and before instrumentation. Of our 105 cases, 21 cases had negative urine cultures on admission, 25 cases had pure E. coli infections and the others had mixed infections representing organisms chiefly of the colon group with staphylococci, streptococci, etc.

The average postoperative stay in the hospital was 14.3 days. A great many of these patients, however, were discharged as early as the seventh postoperative day. The average ambulation period was 2.9 days.

Wound healing was excellent in all patients. Urinary control was good in all cases except one who complained of mild dribbling of urine for as long as 6 weeks after the operation.

Not all of the patients had postoperative residual urine estimated; there was no indication for it in most cases. Of these 105 patients, 53 per cent had clear urine within 3 months after operation. The other 47 per cent had mild to severe infection in the urine for three months or longer. In these we cultured the *B.* aerogenes most commonly. However, even in these patients with persistent postoperative infections only one had a mild residual which has been reduced with treatment. All the others were improved and are now without troublesome symptoms.

SUMMARY

Retropubic prostatectomy is another successful method for the removal of some prostatic obstructions, medium to large glands.

In this approach there is direct vision of the capsule, which can be inspected to see that all of the prostate gland is removed and bleeding stopped.

The vessels of the capsule can be perfectly controlled.

Usually the convalescence is comfortable and the stay in the hospital short.

The postoperative results are excellent.

In this series of 105 there was a mortality rate of 4.7 per cent which should be considerably improved with experience

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REFERENCES

Brooks, S. K.: Retropubic prostatectomy: an extravesical technique: report of 32 cases. J. Urol., 59: 376, 1948.

[illegible], F. A. and Novack, G. J.: Distribution of blood vessels of prostate gland and urinary bladder. Application to retropubic prostatectomy. J. Urol., 62: 663, 1949.

Lavalle, L. L. and Hamm, F. C.: Osteitis pubis: its diagnosis and treatment. J. Urol., 59: 281, 1948.

Lowsley, O. S. and Gentile, A.: Retropubic prostatectomy. J. Urol., 59: 281, 1948.

Millin, T.: Retropubic Urinary Surgery. Edinburgh: E. & S. Livingstone Ltd., 1947.

Millin, T.: Retropubic prostatectomy. J. Urol., 59: 267, 1948.

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EXPERIENCES WITH RETROPUBIC PROSTATECTOMY

W. HOUSTON TOULSON AND (by invitation) HOWARD B. MAYS AND CHARLES W. HAWKINS

It was not until 1948 that we ventured to use retropubic prostatectomy in our clinic. Since this time we have done more than 100 operations by this route.

The patients selected for this procedure were considered to have definite prostate gland enlargements to a grade 2 at least, and all but 5 were thought to be benign. In 2 of the 5 cases the diagnosis was prostatic carcinoma, and in 3 clinical and x-ray evidence of prostatic calculi was present.

The same preoperative care was used in the retropubic operations as in the other types of operations.

The surgical technique which we followed was essentially the same as that described by Millin and emphasized by Bacon and others: "Proper exposure of the retropubic space, gentle dissection, maintenance of a dry field, excision of a section from the posterior edge of the vesical neck, when necessary, thorough hemostasis and adequate repair of the prostate capsule." To this may be added proper postoperative drainage.

About three-fourths of the cases in this series were private patients and the other fourth came from the free wards. Some well calculated risks were taken in this series of patients as with patients usually operated on by other methods.

In this series of 105 patients on whom retropubic prostatectomy was done, there were 5 deaths (4.7 per cent). Three of these deaths were due to coronary thrombosis and 2 to pulmonary emboli.

A high incidence of osteitis pubis has been reported as a distressing complication of this method of operation. Therefore, we have given the greatest consideration to the technique of exposing the prostate gland without traumatizing the periosteum of the pelvic bone either by pressure of retractors or by pricking the periosteum with needles. In our closure we are careful to carry the postoperative drains away from the symphysis pubis, and drain the prevesical space adequately.

None of our patients has so far developed osteitis pubis, nor has obturator neuritis been encountered. This fact we must attribute to the care given the bony structures. We have had no persistent urinary fistulas, no abscess in the prevesical space and no strictures of the urethra, as reported by some operators.

We have had 6 cases of mild postoperative bleeding; all of these patients responded well to the administration of whole blood and fluids. These hemorrhages have occurred as early as several hours to as long as 10 days postoperatively. Postoperative hemorrhage has not been severe enough to require cystotomy. Our experiences with oxycel and gel foam have not been satisfactory.

In this series, 7 per cent of the patients had postoperative epididymitis; two of them had bilateral epididymitis. None of the patients had vas ligation. We believe now we have relied too heavily on chemotherapy to control the infection

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 25, 1950.

occurring in the seminal tract. One of our patients developed a scrotal abscess while on drug therapy, adequate we thought; this required incision and drainage. Culture of the pus from the abscess yielded staphylococci.

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REFERENCES

Bacon, S. K.: Retropubic prostatectomy; an extravesical technique; report of 32 cases. J. Urol., 59: 376, 1948.

Beneventi, F. A. and Noback, G. J.: Distribution of blood vessels of prostate gland and urinary bladder: Application to retropubic prostatectomy. J. Urol., 62: 663, 1949.

Lavalle, L. L. and Hamm, F. C.: Osteitis pubis; its diagnosis and treatment. J. Urol., 59: 281, 1948.

Lowsley, O. S. and Gentile, A.: Retropubic prostatectomy. J. Urol., 59: 281, 1948.

Millin, T.: Retropubic Urinary Surgery. Edinburgh: E. & S. Livingstone Ltd., 1947.

Millin, T.: Retropubic prostatectomy. J. Urol., 59: 267, 1948.

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THE MORTALITY OF TRANSURETHRAL PROSTATIC RESECTION

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This paper has two purposes: to discuss the effect of the use of isotonic irrigating solutions upon the mortality of transurethral prostatic resection, and to compare the risk of open with that of closed operations upon the prostate.

In the former connection, two questions arise: first, does the hemolyzed blood formed in the bladder when plain water is the irrigating solution reach the circulation and, if so, does it do any harm? Anyone can easily see that the addition of water to blood makes a transparent solution, while the addition of an isotonic agent makes a translucent one, and can demonstrate with the microscope that the difference is due to the destruction of red cells in the first instance and to their preservation in the second. Therefore the use of a nonhemolytic solution during transurethral resection requires that the objective of the telescope be held closer to the object than when water is used, in order to minimize the thickness of the translucent layer, and has given rise to the complaint that it makes resection with glucose or glycine impossible. One can reply only that "there is none so blind as he who will not see."

There is incontrovertible evidence that material can pass from the bladder into the circulation during transurethral resection. First is the case of B. K., already reported, who was semistuporous and cyanotic immediately after such an operation, whose plasma was deep red 8 hours later (no transfusion had been given), and who became oliguric, uremic, and jaundiced. Autopsy revealed a typical hemoglobinuric (lower nephron) nephrosis (fig. 1).

Second, a review of sections of the kidneys of 6 patients dying after transurethral resection at the University Hospital during the years 1941 through 1945 disclosed pigmented casts in the tubules in 2 cases.

Third, measurements of the free hemoglobin of the plasma before and after prostatic resection demonstrated that, when water was used for irrigation, the postoperative was 15 times the preoperative level; this has been verified by Landsteiner and Finch, by Bunge and Barer, by Goodwin, Cason, and Scott, and by Robbins et al.; when 4 per cent glucose was used, the pre- and postoperative levels were the same. Moreover, the blood sugar at the end of operation with water in the irrigator was the same as that beforehand; with glucose the blood sugar increased about two and one half times (from an average of 81 to one of 198). This has been verified by Jessop and Lane, who found some correlation between the irrigating pressure and the extent of the rise in the blood sugar.

Next, of 109 cases resected with water, three became jaundiced when no cause other than a hemolytic reaction could be found; no case of janudice has occurred in more than fifteen hundred resections with isotonic solutions.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 25, 1950.

Next, we have found the blood culture positive at the end of transurethral resection in 45 per cent of 350 consecutive cases (Feeney), a figure much higher than that of Biorn, and probably indicative that the resections in this series were more complete (deeper, opening more veins, and lasting longer) than those in Biorn's.

Last, Wear has shown that, if the bladder is distended by diodrast at the end of transurethral prostatic resection and an x-ray is made at once to prove the absence of reflux up the ureters, films exposed subsequently will show excretion of this agent by the kidneys (fig. 2); i.e., diodrast must have entered the circulation by way of the prostatic veins, since the normal vesical mucosa is impermeable to such substances.

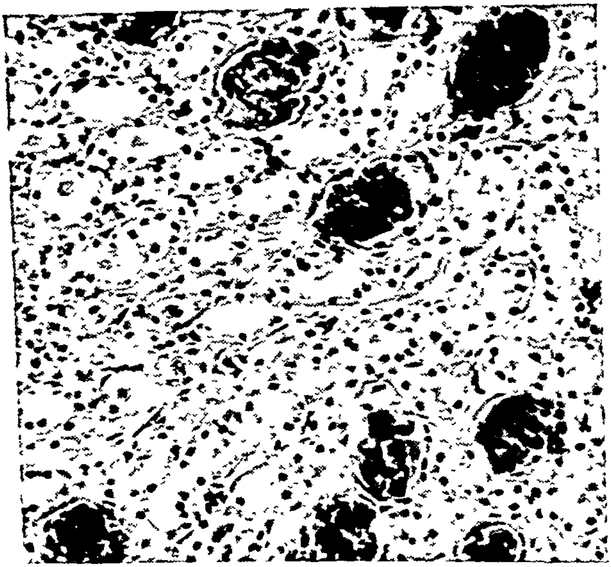

FIG. 1. Pigmented casts in patient B. K., who died following hemolytic reaction due to transurethral resection.

It has been suggested that the entrance of irrigating fluid into the cut prostatic veins can be prevented by using the irrigating fluid under a low head of pressure. This is impossible because so low a pressure would be required that arterial and venous bleeding would obscure vision completely. The use of an isotonic irrigating solution which is a poor electrolyte prevents hemolysis without complications. Four per cent glucose (Creevy), 1.1 per cent glycine (Nesbit) and 3 per cent mannitol (Goodwin, Cason, and Scott) are apparently equally effective.

Granted, then, that free hemoglobin may reach the kidneys when large veins are opened and water containing hemolyzed blood is driven into the circulation, the second question is, does it do any harm? O'Shaugnessy, Mansell, and Sloame injected 50 gm. hemoglobin intravenously into a normal adult. Despite a hemoglobinuria lasting 30 hours, renal function was not demonstrably impaired. Others have made similar observations. Solutions of hemoglobin have been recommended for the treatment of shock, and distilled water is said to have been given intravenously without harm.* Moreover, the level of free hemoglobin required to produce severe renal damage experimentally or in blackwater fever is far higher than any observed after transurethral resection, so why worry?

This reasoning leaves out of account several important factors which undoubtedly come into play during transurethral resection. First of all, it has been shown experimentally by Mason and Mann, by Hesse and Filatov, and by Levy, that the arrival of free hemoglobin in the kidney causes severe renal vasoconstriction. Many prostatics have pre-existing renal damage, (arterio- and arteriolar-sclerosis, pyelonephritis, and hydronephrosis) often advanced, which will presumably intensify the effects of this vasoconstriction.

Further, Corcoran and Page have demonstrated transitory renal damage from the rapid loss of blood even though blood pressure is maintained above "shock" levels; Van Slyke and others have observed impaired renal blood flow from hypotension (anesthesia, shock, hemorrhage) and have shown that protracted profound shock may cause irreversible renal damage; Trueta has made similar observations in severe experimental trauma and after stimulation of the cut end of the sciatic nerve. Franklin has pointed out that distention of the uterus, bowel, or bladder of experimental animals causes renal ischemia by shunting blood from the cortex to the medulla. This is interesting in view of the repeated distension of the bladder which ordinarily accompanies transurethral resection. All of these

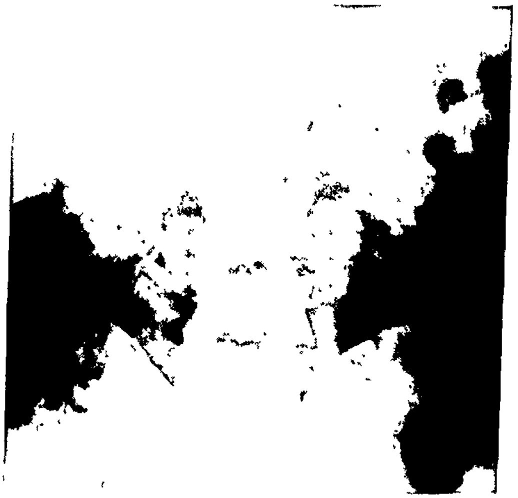

FIG. 2. Excretion of neo-iopax absorbed through prostatic veins at end of transurethral resection.

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* A recent experience of B. J. McGroarty, a former resident in urology at the University Hospitals, suggests that the intravenous injection of distilled water is not innocuous, at least when the kidneys have been damaged. Following a transurethral resection in a patient whose initial uremia from bilateral hydronephrosis had subsided after drainage with a catheter, 300 cc distilled water was given intravenously by mistake, which was discovered only when he had a chill and became cyanotic. The free hemoglobin of the plasma was then 280 mg. per cent, and there was a rise of urea nitrogen with mild jaundice the next day. In other words, an obvious hemolytic reaction occurred and produced measureable impairment of the renal function.

factors are presumed to cause constriction or spasm of the renal vessels, and nearly all may operate to some extent during transurethral resection so that the effect of hemoglobinemia upon the kidney may be greatly intensified.

Yuile, Gold, and Hinds have shown that a pre-existing renal ischemia aggravates the effect of intravenously injected hemoglobin upon the kidneys of experimental animals; Maluf has confirmed this in the case both of severe dehydration and of profound shock; and Goodwin, Cason, and Scott have found that old dogs and those with artificially induced hydronephrosis may suffer more severe renal injury from a given amount of intravenously injected hemoglobin than do young animals with normal kidneys. Add to these the noxious factor of bacteriemia, even though transitory, and it is easy to see how even a moderate hemoglobinemia may be the straw that breaks the camel's back insofar as the kidneys of the prostatic are concerned.

TABLE 1. *Transurethral resection in two series of 100 consecutive patients*

	FIRST HUNDRED	LAST HUNDRED
Age	62.7 yrs.	68.3 yrs.
Preoperative stay	9 95 da.	2.3 da.
Urethrotomy	0	21 %
Tissue removed	5 gm.	44.3 gm.
Per cent repeated	24	21
Carcinoma	16 %	17 %
Blood loss (smallest 0, largest 1000; over 500–9.)	—	180 cc
Hemostasis, early	2%	1%
Hemostasis, late	1%	2%
Postoperative stay	12.1 da.	10.3 da.
Mortality, per cent	4 0	0

These theoretical considerations are all very well. What about the practical proof? Table 1 gives the details of the writer's first hundred transurethral resections (before isotonic solutions) and of his last hundred ending February 2, 1950. Notable differences in the two series include the more advanced age, the shorter preoperative hospitalization, the great increase in the amount of tissue removed, and the absence of mortality in the second series. The continued high percentage of repeat operations is due to pessimism, and to unwillingness to discharge a patient with difficult micturition or residual urine. The postoperative hospital stay in the second series while shorter than in the first, is longer than that reported by many others chiefly because of the high proportion of two stage operations, and because nearly all of the patients come from out of the city.

More significant than these figures is table 2 which gives, among other things, the mortality of transurethral resection in a thousand consecutive cases done by the writer and his two former associates (Drs. E. A. Webb and B. A. Smith, Jr.) since the adoption of isotonic irrigating solutions. The mortality of 0.6 per cent is about as low as one can rightfully expect in operations upon elderly men; it seems reasonable to suppose that the difference between this mortality and that of the others shown in the table is due to the use of isotonic irrigating fluid.

TABLE 2. *Mortality of operations upon the prostate*

AUTHOR	YEAR	TYPE	CASES	MORTALITY
				Per cent
Nesbit	1946	TUR	2425	1.81
Thompson	1948	TUR (punch)	11,522	1.20
Creevy, Webb, Smith	1950	TUR	1000	0.60
Total			14,947	1.29
Residents, U. of Minn.	1950	TUR	560	2.50
Whole Series, U. of Minn.	1950	TUR	1560	1.20
Young	1926	Perineal	1000	3.20
Barney	1936	Perineal and SP	816	14.20
Hunt and Walters	1938	Suprapubic	1000	5.40
Millin	1949	Retropubic	757	4.50
Total			3573	6.60

TABLE 3. *Mortality of enucleation of prostate, 1945–1949*

Esersky and Greenberg	1945	SP	50	1
Zimmerman	1946	SP	51	2
Rees (England)	1947	SP	242	23
Rees (England)	1947	P	45	4
MacDonald (Canada)	1947	SP	495	39
Morville (Denmark)	1947	RP	20	2
Brunner (Switzerland)	1947	RP	51	2
Stock (England)	1947	SP	40	1
Derycke (Belgium)	1947	RP	22	1
Goldstein	1947	P	36	1
Eikner	1948	SP	89	1
Treiger et al	1948	SP	108	9
McCrea	1948	SP	100	4
Grant, Lich et al.	1948	RP	65	0
Lowsley et al	1948	RP	20	0
Galbraith (England)	1948	SP	318	12
Ward (England)	1948	VC	50	2
Walters (England)	1948	ASP	115	9
Jacobs (Scotland)	1948	RP	205	15
Bacon	1949	RP	102	7
Weijlandt (Holland)	1949	RP	60	3
Higbee	1949	P	336	6
Presman and Rolnick	1949	RP	40	3
Total			2760	147
Operative mortality				5.3%

In any case, the table shows a mortality of 1.29 per cent in a total of 14,947 patients from three sources subjected to transurethral resection with and without nonhemolytic solutions.

Contrast this with the mortality for the various open operations shown below: 6.6 per cent in 3573 cases. This invidious comparison is prompted by recent statements here and there in the literature to the effect that the mortality of the open operations is now no greater than that of transurethral resection, and citing a small series of cases in support of this contention, although every surgeon of experience knows that the mortality of a small series may, owing to the operations of chance, be quite different from that in a large group, in which chance variations are necessarily smaller. It is conceded that the series of retropubic prostatectomies of Millin is the only large one reported since the advent of antibiotics, improved methods of anesthesia (most of our cases were done with old fashioned spinal), and the free use of transfusion, but no other recent large series of open operations has been found. It has, however, been possible, by culling many smaller series from the literature between 1945 and 1950 to collect 2435 open enucleations (table 3). Notwithstanding the fact that several of the authors reported small groups without deaths, the overall hospital mortality was 5.3 per cent, and this since the advent of antibiotics, widespread use of transfusion, and "modern methods of anesthesia".

The five hundred odd cases done by the residents at the University Hospitals since the adoption of isotonic irrigating fluid are listed separately, not to make the mortality of the other series lower, but to point out that men learning transurethral resection with nonhemolytic solutions on patients who are, on the average, very poor risks, achieve a mortality lower than that ordinarily attained by many experts with the open operations.

SUMMARY AND CONCLUSIONS

Free hemoglobin formed in the bladder by contact between blood and the water used as irrigating fluid during transurethral prostatic resection may be driven into the circulation when large prostatic veins are opened.

When this free hemoglobin reaches the kidneys, renal vasospasm results and may lead to severe or fatal renal damge, particularly in the presence of rapid loss of blood, hypotension, bacteriemia, or pre-existing renal damge.

This reaction is prevented by the use of an isotonic irrigating solution (glucose, glycine, mannitol), thereby lowering the morbidity and mortality of transurethral resection of the prostate.

A series of 1000 consecutive cases in which transurethral resection was done with glucose and glycine as the irrigating solutions is reported, the surgical mortality being 0.6 per cent.

The mortality of transurethral resection is far below that thus far reported for any of the open methods of enucleating the enlarged prostate.

The statement that the mortality of open enucleation of the prostate is no greater than that of transurethral resection (if well done) is not warranted up to the present time.

REFERENCES ON HEMOLYTIC REACTIONS

Baird, S. S. and Spence, H. M.: Lower nephron nephrosis after transurethral prostatic resection. Urol. & Cut. Rev., 51: 642, 1947.

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Biorn, C. L., Browning, W. H. and Thompson, L.: Transient bacteriemia immediately following transurethral resection. J. Urol., **63:** 155, 1950.

Bunge, R. G. and Barer, A. P.: Hemolysis during transurethral prostatic resection. J. Urol., **60:** 122–123, 1948.

Credle, W. S.: The injudicious use of urea in irrigating solutions during prostatic resection. In press, Journal of Urology.

Creevy, C. D. and Webb, E. A.: A fatal hemolytic reaction following transurethral resection of the prostate gland, Surg., **21:** 56–66, 1947.

Creevy, C. D.: The importance of hemolysis during transurethral prostatic resection; a clinical investigation. J. Urol., **59:** 1217–1232, 1948.

Dees, T. A., Stewart, W. D., Meares, E. F. and Orr, L. M.: Modified irrigating solution for transurethral prostatic resections: a preliminary report. J. Urol., **59:** 212, 1948.

Ebert, C. E.: A clinical comparison of the use of glucose and urea in irrigating solutions for transurethral prostatic resections. J. Urol., **62:** 736–741, 1949.

Evert, R. N. and Creevy, C. D.: Hemolysis during transurethral resection. Bull. Univ. of Minn. Hospitals, **21:** 229–236, 1950.

Feeney, M. J. and Creevy, C. D.: Infection following transurethral resection of the prostate gland. Bull. Univ. of Minn. Hospitals, **20:** 314–327, 1949.

Franklin, K. J.: In discussion on the pathological features of cortical necrosis of the kidney. Proc. Roy. Soc. Med., **42:** 380, 1949.

Garske, G. L., Phares, O. C. and Sweetser, T. H.: The status of irrigating fluids for transurethral resection: our experience and a survey of various solutions by others. J. Urol., **62:** 322–327, 1949.

Goodwin, W. E., Cason, J. F. and Scott, W. W.: Hemoglobinemia and lower nephron nephrosis following transurethral surgery. In press, Journal of Urology.

Griffin, M.: Toxic symptoms accompanied by hemolysis during transurethral prostatectomy. J. Urol., **59:** 431–436, 1948.

Jessop, W. J. E. and Lane, T. J. D.: Uremia: a survey of some recent developments. Irish J. Med. Sc. Series, **6:** 707, 1948.

King, K. B. and Werner, J. R.: Lower nephron nephrosis complicating transurethral resection; some clinical observations. Trans. South Central Sect. Am. Urol. Assoc., p. 83, 1947.

Landsteiner, E. K. and Finch, C. A.: Hemoglobinemia accompanying transurethral resection of the prostate. New Eng. J. Med., **237:** 310–312, 1947.

Maluf, N. S. R.: Factors inducing renal shutdown with lysed erythrocytes. Ann. Surg., **130:** 49, 1949.

McGinn, E. J., Miale, J. B. and Frye, J. W.: Hemoglobinuric nephrosis in transurethral prostatic resection; treatment by peritoneal lavage. Urol. & Cut. Rev., **52:** 509–514, 1948.

McLaughlin, W. L., Holyoke, J. A. and Bowler, J. P.: Oliguria following transurethral resection of the prostate gland. J. Urol., **58:** 221–234, 1947.

Nesbit, R. M. and Glickman, S. J.: The use of glycine solution as an irrigating medium during transurethral resection. J. Urol., **59:** 1212–1216, 1948.

O'Brien, H. A., Mitchell, J. D., Jr. and St. Martin, E. C.: Transurethral resection of large prostates. J. Urol., **62:** 225–230, 1949.

O'Brien, H. A. and Mitchell, J. D., Jr.: Hemolysis during transurethral resection. Trans. South Central Sect. Am. Urol. Assoc., pp. 89–92, 1947.

Robbins, M. A., Olson, W. H. and Rolnick, H. C.: Clinical observations on use of hemolytic and nonhemolytic irrigating medium for transurethral prostatic resection. Surg., **27:** 254, 1950.

Sjostrand, T.: Endogenous formation of carbon monoxide in man under normal and pathological conditions. Scand. J. Clin. & Lab. Investig., **1:** 201, 1949.

Wear, J. B.: Some observations on the technique of transurethral prostatic resection. J. Urol., **62:** 470–473, 1949.

Wardill, W. E. M.: Benign enlargement of the prostate (Med. Soc. of London, discussion). Brit. J. Urol., **18:** 72, 1946.

Woodruff, L. M. and Firminger, H. J.: Hemoglobinemia and hemoglobinuric nephrosis complicating transurethral resection of the prostate. J. Urol., **62:** 168–177, 1949.

REFERENCES ON MORTALITY OF OPEN OPERATIONS

Barney, J. D.: Twenty-five years of urology. Tr. Am. Assn. G. U. Surg., **29:** 285, 1936.

Hunt, V. C. and Walters, W. A.: Suprapubic prostatectomy: report of one thousand cases. Surg., Gynec. & Obst., **46:** 769, 1938.

Millin, T.: Retropubic prostatectomy. Lancet, **1:** 381, 1949.

Young, H H. and Davis, D. M.: Young's Practice of urology. Philadelphia: W. B. Saunders Co., 1926, vol. 1, p. 496.

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RELATIONSHIP OF STEROIDS TO SOME PROBLEMS IN PROSTATIC CANCER AND TO MEDICINE IN GENERAL

WILLIAM P. HERBST

One of the earliest types of endocrine therapy was the use of virgins' urine as a medicinal agent. In 1893, castration was inaugurated for prostatic hypertrophy in the male and for malignancy of the breast in the female. In 1941, administration of estradiol diproprionate was reported by me and castration by Huggins in the treatment of prostatic cancer. Huggins also demonstrated that androgen stimulated and estrogen inhibited prostatic epithelial cells either benign or malignant.

CLINICAL OBSERVATIONS

For mental depression, estrogen or androgen has been used for both sexes.

Vasomotor instability in either sex due to gonadal insufficiency has been fairly well controlled by the administration of either estrogen or androgen.

Testosterone has been used as a morale builder for patients who face either single or multiple surgical procedures and do not seem to have the nerve to be operated upon.

Psychogenic amenorrhea, as reported by Reifenstein, has been found to be accompanied by a decrease in the urinary excretion of the 17-ketosteroids.

British surgeons observed a steroid insufficiency insofar as impotence was concerned. They found that patients on whom they were going to do prefrontal lobotomies had practically zero 17-ketosteroids and were impotent. After they had the prefrontal lobotomy, the patients became potent and the ketosteroids returned to normal again.

Stress and lack of oxygen produced hyperadrenal secretion of cortisone or compound E through the effect of hypothalmas.

The phenomenon of fainting is an inhibition of the secretion of the adrenals.

The instances of success in producing pregnancy by couples who have adopted children are strongly suggestive of a change in the steroid balances.

The observation that many individuals who are producing oxalate gravel do not produce these gravel when they are living under conditions without stress, whereas when they are living under stress they continue to form these oxalate gravel, is indicative of changes in steroid balance.

All of the above observations present enough correlation between psychic influences to make the name "psychosomatic medicine" obsolete and definitely unscientific. Instead of psychosomatic medicine, "psychochemical medicine" would be much more appropriate.

FURTHER OBSERVATIONS ON THE CLINICAL RESPONSE TO CERTAIN OF THE STEROIDS

Testosterone has been observed to favorably modify the cardiac muscle metabolism and to result in the relief of certain arrythmias. In some instances

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 25, 1950.

people who are definitely victims of senile dementia can be brought back in satisfactory contact with their environment upon the administration of testosterone.

Unfreshened cows can be made to yield milk when given stilbestrol.

Testosterone favorably influences breast carcinoma in the female.

Old race horses have been rejuvenated and made winners by the administration of testosterone.

Diabetes is favorably influenced by estrogen or castration.

Patients who suffer from rheumatoid arthritis are spectacularly relieved and we see tissue changes reversed in them which were previously considered irreversible following the administration of cortisone or ACTH.

In the field of acute bacterial infectious and inflammatory lessions we see almost instant relief of fever and inflammation following the administration of cortisone or ACTH.

CHEMISTRY

The testis excretes nine steroids. The ovary excretes four, the placenta three and the adrenal not less than twenty-eight, one of which is cortisone. Forty-six steroids have been identified in the urine. Dobriner has made numerous pattern analyses of a moderate number of the steroids excreted in the urine of normal people and in patients who are suffering from different malignant and nonmalignant clinical entities to determine if such patterns could be of value in diagnosing these entities. To date he has observed that the amount of etiocholanolone is strongly suggestive of malignancy.

It has been observed that small doses of testosterone cause atrophy of seminiferous epithelium, whereas large doses protect spermatogenic elements against atrophy.

The effect of testosterone, estradiol and progesterone on vaginal cornification, seminal vesicle growth and progestation provides a pattern which insofar as specificity of action is concerned is most interesting.

Epinephrine, stress and lack of oxygen produce hypothalmic stimulation of the anterior pituitary which produces ACTH which in turn stimulates the adrenal to produce cortisone, and results in a decrease in the eosinophile count.

Block and Rittenberg have demonstrated that acetates arise from oxidation of fatty acids and cholesterol by labeling carbon atoms. This observation opens up a metabolic mechanism which may be related to oxalate stone formation in that the organic acid series involving the acetates, citrates, oxalates, malates, etc., are intimately related.

Along this same line it is significant that estrogens produce an increase in citrate urinary excretion or secretion as the case may be.

The study of urinary steroid pattern analysis, while very interesting, involves the functional state of the kidney and therefore is subject to certain inaccuracies. The blood pattern analysis would be much more dependable, but even blood analyses leave much to be desired insofar as our ability to determine accurate specificity of action on different tissue cells.

The studies on tissue culture offer a much better controlled type of observation, but obviously this type of observation cannot be utilized in most of our clinical problems.

In conclusion, steroid chemistry which was given such an impetus by our observations and experience with estrogen therapy and castration in the treatment of prostatic carcinoma, has now spectacularly influenced numerous other medical fields and gives promise of further valuable therapeutic applications.

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PRELIMINARY REPORT ON THE CLINICAL USE OF TACE (CHLOROTRIANISENE) IN TREATMENT OF PROSTATIC CARCINOMA

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At the beginning of the present century orchiectomy was recommended and frequently used as a method of treatment of vesical neck obstruction diagnosed as prostatic hypertrophy. The continued use of this method of treatment for more than a decade was probably due to the beneficial effects obtained in certain cases of carcinoma of the prostate that had been mistakenly thought to be prostatic hypertrophy.

For over 30 years there have been advocates of the use of oophorectomy as a part in the treatment of the carcinoma of the breasts of the female. For many years we have been aware that the presence or absence of gonadal tissue affects the incidence of carcinoma of the breast in standardized carcinoma bearing strains of white mice.

In spite of these and other equally significant sign posts, indicating the channels our thinking should follow, it was only 10 years ago that one of our own members called our attention to the value of hormonal therapy in the treatment of prostatic carcinoma. We, of course, refer to the monumental work of Huggins.

The brilliance of his work forcibly called our attention to the beneficial effect obtained in the treatment of carcinoma of the prostate by the administration of estrogens and, or, the diminution of the androgens following castration. A change in the androgenic-estrogenic balance in favor of the androgenic phase has been interpreted as being the etiological factor producing prostatic carcinoma. The almost immediate and particularly spectacular results obtained by applying the principle of hormonal therapy to those suffering from carcinoma of the prostate so impressed all of us that it very promptly became the method of treatment of this condition that was used by all informed physicians.

As time went on, and we had the opportunity of following these patients, we learned that the spectacular improvement following the initiating of this plan of therapy was at times extremely transitory and only infrequently was it of permanent character. We then began to vary the manner in which we used the agencies of hormonal therapy viz: castration and estrogen administration with the result that although we agree in principle there is a great divergence of opinion as to what plan should be followed in applying that principle in the treatment of carcinoma of the prostate.

Recently, we had the opportunity to ask a number of our friends to inform us about the course of treatment they were using. Although we were aware there was a difference of opinion among us, we had no idea we would receive as

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The material used in this study was supplied by the Wm. S. Merrell Company, Cincinnati, O., under its trade name "Tace."

many different plans of therapy as replies to our request. Some recommended the use of orchiectomy as an initial phase of the treatment and others strongly advocated that orchiectomy be reserved for use as a means of last resort. Practically everyone prescribes stilbestrol and there was a general unanimity of opinion that its administration should be more or less continuous throughout the rest of the patient's life, but the variation in the recommended size of the daily dose was really astounding: it varied from 1.5 mg. to 600 mg. per day. Certainly there is no other commonly used principle of therapy whose method of application varies as widely as this.

There is only one conclusion that can be drawn when such a situation is analyzed, and that is, there is no general knowledge of the sequence of events that precede and follow the development of carcinoma of the prostate and the carrying out of hormonal therapy.

We believe that it is time for us to pause and make a real search of our fund of knowledge in the hopes that we recognize certain proven facts or worthy observations that can at this time serve as sign posts needed to guide us in our thinking.

To us there are two facts that we believe do qualify in that respect and should receive serious consideration.

First, most of us are definitely convinced, and we believe correctly so, that at least a contributing factor, if not the real cause of the retrogression of prostatic carcinoma, is hyperactivity of the hormonal phase of adrenal function. Actual hyperplasia of that organ has been reported as an autopsy finding of persons dying as a result of this recrudescence. This fact has been of sufficient importance to some of us to prompt us to attempt to counteract this hyperactivity by such procedures as adrenalectomy, radiation of the adrenal or of the pituitary.

A fact that is of equal importance, especially when considered in conjunction with the preceding observations, is that the continued administration of the estrogens, hexestrol and stilbestrol to laboratory animals, causes enlargement of the adrenal and pituitary. It is possible that estrogenic therapy as prescribed by most of us may be a factor favoring this recrudesence by producing a similar adrenal hyperplasia in man. We might also point out that castration of male rats also causes enlargement of these organs, although only to a minimal degree.

An understanding of this problem of recrudescence of prostatic carcinoma, which of course is of prime importance to all of us, can be approached by obtaining a more complete knowledge of the role played by the adrenal. We believe that an intensive study of the ketosteroids as they occur in patients with carcinoma of the prostate, especially in those receiving hormonal therapy is indicated. Analysis of assay determinations of these ketosteroids, particularly the beta fraction of the 17-ketosteroids, may give us a basis for a more accurate prognosis—may provide us with the means of more scientifically planning a course of hormonal therapy and should be of diagnostic value.

Because adrenal hyperplasia seems to be a matter of importance in those patients in whom recrudescence of prostatic carcinoma occurs, it would appear that we should devise a plan of therapy that would delay this development or lessen or even prevent the likelihood of its occurrence. It is for that reason that we wish to make a brief preliminary report on our clinical experience in the treatment of carcinoma of the prostate with a new synthetic estrogen, for there are indications that it may serve such a purpose.

About two years ago we were given the opportunity to initiate a program of clinical investigation of the usefulness of the synthetic estrogen, Tace (chlorotrianisene) in the treatment of carcinoma of the prostate. This estrogen, tri p-anisylchloroethylene is chemically similar to diethylstilbestrol and hexestrol in that the three compounds have two phenyl groups separated by two carbon atoms. These carbon atoms are saturated in hexestrol and unsaturated in Tace and diethylstilbestrol. Tace also differs from diethylstilbestrol and hexestrol in that, instead of two hydroxyphenyl groups, it has two methoxyphenyl groups and the two ethyls are replaced by a methoxyphenyl and a chlorine group. See figure 1.

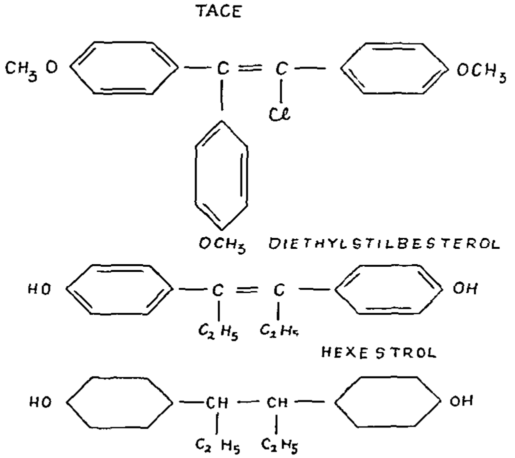

Figure 1

In the beginning of the investigation, we prescribed Tace only to those patients in whom a continuance of diethylstilbestrol therapy seemed inadvisable. It was immediately apparent that the physical evidence (such as gynecomastia and the findings on rectal examination) of the effectiveness of diethylstilbestrol therapy in those patients was easily maintained by Tace and that it did not produce gastric irritability. Prior to our clinical investigation of this synthetic hormone, the research staff of the company interested in Tace carried on an extensive investigative program on laboratory animals. At one of our conferences early in the course of this investigation, they reported that Tace, unlike stilbestrol and hexestrol, produced only minimal enlargement of the adrenal and no enlargement of the pituitary gland in laboratory animals even when given in large dosage over a long period of time. The importance of that fact is immediately apparent and aroused our enthusiasm to continue our clinical investigation on a much wider scope. The findings referred to above have already been reported in a preliminary manner and are the subject of a detailed report, being published elsewhere by the members of that research staff.

We have divided our series of 64 patients into four groups. All of these 64 cases are private patients and consequently we have an adequate follow-up study.

Group 1 is composed of 19 patients, who upon rectal examination showed physical findings of carcinoma of the prostate. Following the administration of Tace, a regression or disappearance of those findings has been noted. Medication is being continued in this group. They have all been greatly improved and those who have been under observation for a sufficient period of time to warrant a deduction have little if any physical evidence of carcinoma of the prostate. Obviously biopsies have not been obtained on this group for they are what might be called early cases.

Group 2 is composed of 21 patients in whom the physical evidence of carcinoma of the prostate as determined by rectal examination was obvious. Many of them were in retention. They were all hospital patients and all were improved by the administration of Tace as an initial procedure. Because we believe in early orchiectomy, they have all been castrated and are being continued on Tace medication. Of the 21 cases, the diagnosis has been confirmed by biopsy in 14. Their improvement has been equal to, if not greater than, that seen with other plans of therapy. So far none of them has shown any tendency to recrudescence, but it must be remembered that they have been under observation for no longer than 18 months.

Group 3 is composed of 17 cases who have been under observation for a period varying from 3–7 years. All were under treatment prior to the beginning of the investigation. All were castrated at the beginning of treatment and were kept on stilbestrol until changed to Tace. Bone metastases were present in 11 when the diagnosis was made, 12 have positive biopsies, all had marked urinary difficulty, 12 were in retention.

This group represents the rather far advanced cases which we would expect to show a definite recrudescence of their prostatic condition, irrespective of the plan of therapy used. So far, in only 2 of these cases have the patients shown evidence of recurrence: one, who had metastases at the beginning of treatment 6 years ago, has just died and another who also had metastases when first seen has after 4 years just recently developed a marked extension of his metastases.

The last group, composed of 7 cases, is similar to the above except that they are in the terminal phase of the disease. They were not changed from stilbestrol to Tace until after recrudescence was evident. Tace has been of little benefit in these cases.

In conclusion we feel justified on the basis of our encouraging preliminary observations in enlarging our studies on the new synthetic estrogen, Tace, in the palliative treatment of carcinoma of the prostate.

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REFERENCES

Thompson, C. R. and Werner, H. W.: A comparison of two synthetic estrogens, tri-p-anisylchloroethylene and hexestrol. Federation Proc., 4: 139, 1945.

Thompson, C. R. and Werner, H. W.: Studies on the fate of tri-p-anisylchloroethylene and hexestrol. Federation Proc., 5: 208, 1946.

Thompson, C. R. and Werner, H. W.: Studies on tri-p-anisylchloroethylene, a new synthetic estrogen. To be published.

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MANAGEMENT OF OCCULT PROSTATIC CARCINOMA

REED M. NESBIT AND WILLIAM C. BAUM

The rational clinical management of occult prostatic carcinoma has always offered the urologist a problem in therapy, solved in most instances by the practice of conservative observation rather than further radical extirpation of the entire gland and its adnexal structures. Many physicians have used this regimen in the belief that most of these patients live their normal life expectancy without the development of the evident features of prostatic malignancy.

Moore, Baron and Angrist, and others have emphasized the relatively high incidence of occult prostatic carcinoma in their studies of men past the age of 40 who came to postmortem examination. Considering the frequency with which they found unsuspected prostatic neoplastic activity, it is surprising that the proportion of men who present themselves for the diagnosis and therapy of prostatism, and who are subsequently found to have cancer of the prostate, is not materially higher. One is forced to conclude that from the standpoint of pathogenesis, these occult tumors seem to possess a different pattern or rate of cellular activity than those whose origin is in the posterior lamella, and which are commonly recognized on digital rectal examination. Most practitioners are acquainted with the usual rapid progress of this classical lesion when left untreated. Nesbit and Plumb have shown that even in those who present no evidence of metatases when first seen, the average survival is but 24.7 months from the time of initial diagnosis.

If it be true that the prostate is capable of playing host to two types of adenocarcinoma, having at least different clinical characteristics, must we then develop a philosophy of therapy to fit each circumstance? The choice of radical perineal prostatectomy for the early palpable carcinoma limited to a small area within the capsule has become accepted practice, for it has been shown that surgical removal offers the only real opportunity for cure in such instances. But should this principle be extended to include all cases of occult carcinoma found after transurethral, suprapubic, retropubic or simple perineal prostatectomy? The Hinmans in a recent publication have suggested that such a program be established and have presented interesting data in a small closed series of cases to support their contention that a survival advantage is apparent when simple prostatectomy is followed by radical surgery should the original tissue removed show evidence of clinically unsuspected neoplastic activity.

These results are somewhat at variance with the published findings of G. J. Thompson of the Mayo Clinic who reported a 60.9 per cent 5 year survival in 112 patients in whom clinically unsuspected adenocarcinoma was discovered following transurethral prostatectomy. It was our impression that the experience of Thompson paralleled that of this institution. As a result, we were stimulated to investigate the survival of 63 patients seen in the University Hospital in the past 16 years in whom a diagnosis of prostatic carcinoma was made after pros-

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tatectomy and similarily was unsuspected prior to operation. Forty-two of these patients were followed in sufficient detail to allow accurate clinical evaluation of their progress following therapy. The results of this survey are presented in the following paragraphs.

AGE DISTRIBUTION

The average age of the individual on whom this pathological diagnosis was made was found to be 74 years. The youngest was 52, the oldest 88.

PRESENTING SYMPTOMS

In all cases the presenting symptoms were those of prostatism. In 2 cases this was complicated by hematuria for which no cause was found but benign prostatic hypertrophy with associated venous engorgement. The average duration of symptoms was 1½ years and varied from less than 1 week to 8 years.

FINDINGS ON EXAMINATION

In all cases but two the prostate gland was described as clinically benign in character and averaged 1 plus in estimated size. Two cases were considered to be suspicious of carcinoma by at least one examiner and both were found to have grade 2 adenocarcinoma infiltrating most of the tissue submitted. One of these patients died 18 months after diagnosis and the other is alive after 31 months of observation, free from symptoms. Neither case truly falls in the occult classification.

X-RAY FINDINGS

Examination of the bony pelvis and lumbar spine by x-ray was carried out in 29 of the 41 cases and in all instances showed no abnormalities attributable to prostatic carcinoma.

LABORATORY FINDINGS

Serum phosphatase determinations were made on 22 of the 41 patients in each case were within normal limits.

CHARACTER OF THE TISSUE REMOVED

An average of 32 gm. of tissue was removed from each case. The microscopic sections were reviewed in all instances, and the areas characteristic of carcinoma identified. From the histological standpoint this material did not constitute a homogeneous group. In many instances there were localized changes which would lead to a diagnosis of well differentiated, or grade 1 adenocarcinoma. In a less numerous group, small foci of less well differentiated carcinoma were found. The factor common to all of these was the conviction on the part of the pathologist that a diagnosis of carcinoma was justified.

SURVIVAL DATA

Twenty six of the 42 patients followed remained alive and free from symptoms. Fourteen of the 42 patients died of causes other than prostatic carcinoma, and as near as can be determined, were free from symptoms attributable to prostatic cancer at the time of their demise. Two of the 42 patients died of prostatic cancer; one, 18 months after diagnosis, and the other, 168 months after first examination. The survival data on the 26 patients still alive are enumerated in table 1.

TABLE 1. *Survival data on 26 patients with occult prostatic carcinoma discovered following transurethral prostatectomy*

MONTHS SURVIVAL SINCE ORIGINAL DIAGNOSIS	NUMBER OF PATIENTS	PER CENT		
148	7 patients with greater than five year follow-up.	26% 5 yrs.	46% 4 yrs.	65% 3 yrs.
144				
104				
102				
84				
72				
66				
52	5 patients with greater than four but less than five year follow-up.			
51				
51				
49				
48				
43	5 patients with greater than three but less than four year follow-up.			
43				
38				
36				
36				
31	9 patients with less than three year follow-up.			
30				
30				
30				
27				
27				
24				
20				
18				

DISCUSSION

Admittedly the number of cases available for presentation here is small, and without significance, in the statistical sense of the word, from the standpoint of survival, for they do not represent a closed series for purposes of follow-up. It is hoped that these may be added to those from other clinics for statistical analysis at a later date. Nevertheless, it would seem that there is justification in assigning some importance to the fact that of 42 patients with occult prostatic carcinoma, only 2 subsequently died of this disease. At least 65 per cent of the 26 patients alive and free from symptoms at the time of the survey had been followed for 3 years or longer.

It should be of some interest to compare these results generally with those previously reported with various therapeutic programs in patients with proven prostatic carcinoma, but with no evidence of metastases at time of first examination (table 2).

Attention is at once drawn to several facts of interest in making this comparison. It would appear that endocrine therapy, particularly when orchiectomy and estrogens are employed, offers almost as great an oppotunity for 5 year survival as does radical perineal prostatectomy. This fact becomes even more significant when it is realized that the cases utilized for comparison in the series treated by radical surgery constitute a highly select group whose carcinoma by selection was limited to a small area in the posterior lobe, while those treated by endocrine therapy all had palpable extension of the neoplasm into the periprostatic tissues when first examined. The results of Thompson are superior to both the endocrine treated cases and those submitted to radical perineal prostatectomy. His cases, like those included in the present report can be regarded as within the category of "occult carcinoma".

TABLE 2. *Comparison of 5 year survival with various therapeutic programs in patients with prostatic carcinoma who show no evidence of metastases on first admission*

CLINIC	NUMBER OF PATIENTS	BASIS FOR DIAGNOSIS	TYPE OF TREATMENT	PER CENT FIVE YEAR SURVIVAL
Nesbit and Plumb	273	Palpable clinical carcinoma with positive tissue diagnosis.	None (control)	22%
Nesbit and Baum	324	Palpable clinical carcinoma with positive tissue diagnosis.	Endocrine therapy	
			Stilbestrol	29%
			Orchiectomy	31%
			Stilbestrol and orchiectomy	44%
Colston	38	Palpable small nodule in posterior lamella with positive tissue diagnosis.	Radical perineal prostatectomy	50%
Colby	14			35%
Jewett	78			50.9%
Young	33			50%
Thompson	112	Clinically unsuspected. Carcinoma found in tissue removed at transurethral prostatectomy.	Transurethral prostatectomy only	60.9%

The average age of the patient found to have prostatic carcinoma in over 2500 cases reviewed by Nesbit and Plumb, and Nesbit and Baum is 70 to 74 years. From the Metropolitan Life Insurance statistics the normal life expectancy at this age is from 7.4 to 10.3 years. These men present themselves at a period of life when they are most anxious to enjoy the fruits of existence, a period when personal comfort is paramount, and in many cases at a time when society can best benefit from the experience they may offer as a result of personal attainment in particular fields of endeavor. Are we justified therefore in prostatic cancer at the time of their demise. Two of the 42 patients died of prostatic cancer; one, 18 months after diagnosis, and the other, 168 months after first examination. *The survival data on the 26 patients still alive are enumerated* in table 1.

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REFERENCES

Baron, E. and Angrist, A.: Incidence of occult adenocarcinoma of the prostate after 50 years of age. Arch. Path., **32**: 787–793, 1941.

Buchert, W., Culp, D. A. and Jones, G. H.: Carcinoma of the prostate: An analysis of 135 cases. Penn. Med. J., **51**: 165–172, 1947.

Colby, F. H.: Carcinoma of the prostate. Total perineal prostatectomy. Surg. Cl. of N. Am., pp. 1307–1312, Oct. 1947.

Colston, J. A. C.: Surgical treatment of carcinoma of the prostate. N. Eng. J. Med., **223**: 205–214, 1940.

Hinman, F. and Hinman, F., Jr.: Occult prostatic carcinoma diagnosed upon transurethral resection. J. Urol., **62**: 723–729, 1949.

Kahler, J. E.: Carcinoma of the prostate gland; pathological study. J. Urol., **41**: 557–574, 1939.

Jewett, Hugh J.: Radical perineal prostatectomy for carcinoma of the prostate: An analyses of 190 cases. J. Urol., **61**: 277–280, 1949.

Moore, R. A.: The morphology of small prostatic carcinoma. J. Urol., **33**: 224–234, 1935.

Nesbit, R. M. and Plumb, R. T.: Prostatic carcinoma. Surg., **20**: 263–272, 1946.

Nesbit, R. M. and Baum, W. C.: A clinical and statistical study of endocrine therapy in 1818 cases of prostatic carcinoma. J. A. M. A., **143**: 1317–1320, 1950.

Smith, G. G.: Total perineal prostatectomy. Penn. Med. J., **44**: 1391–1399, 1941.

Statistical bulletin of the Metropolitan Life Insurance Company, **30**: 1–3, 1949.

Thompson, G. J.: Transurethral resection of malignant lesions of the prostate gland. J. A. M. A., **120**: 1105–1109, 1942.

Young, H. H.: Carcinoma of the prostate: radical cure. Am. J. Surg., **28**: 32, 1936.

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ELECTIVE RESECTION OF CERTAIN URETHRAL STRICTURES

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The treatment of inflammatory and traumatic strictures of the urethra by gentle, periodic dilatation has been in general usage for a great many years, and is unquestionably the treatment of choice in the majority of instances. However, there are certain strictures of the urethra which possess characteristics of elasticity, contour, or impassability, and in these the aforementioned therapy leaves much to be desired. Some of these fall into a category which allows their elective total surgical removal, followed by primary urethral anastomosis. This paper will deal with the criteria for surgery, with the operative technique employed, and with the results obtained.

SELECTION OF CASES

It is difficult to anastamose the urethral stumps if a segment longer than 1½ inches is removed; hence strictures of greater length than this are usually not subjected to resection. Similarly an excessive peri-urethral induration with perineal fixation contraindicates operative removal. Strictures which are less than 1½ inches in length and which do not have excessive fixation are technically suitable for surgical removal. Urethral dilatation is always used first; and when symptoms are not relieved after adequate trial, or when dilatation is necessary at such frequent intervals as to make this clinically undesirable, surgery is given consideration. The failure of dilatation to effect relief of symptoms is usually due to one or more of the following factors: an elastic stricture which dilates rather easily but which also recontracts rapidly; a rigid stricture which resents dilatation, however, gentle; and false passages, pockets, and diverticula of the urethra in the vicinity of the stricture. Urethrograms are made in all patients and we feel that this procedure gives the most definite evidence as to the resectability of a stricture, as well as being an excellent permanent record useful in evaluating the result.

TECHNIQUE OF OPERATION

The patient is placed in the exaggerated lithotomy position; a perineal table facilitates the exposure. A sound is passed into the urethra down to the point of stricture (fig. 1). Incision is made in the midline at this point and carried posteriorly to a point 1 inch anterior to the anal margin. The bulbocavernosus muscle is exposed and incised in the midline, over the palpable stricture. In the case of a stricture located at the bulbomembranous junction, the bulb can often be retracted anteriorly without incision. There is usually some bleeding when the bulbocavernosus is incised, and these bleeders are ligated with fine catgut. The edges of the bulbocavernosus muscle are retracted laterally and by scissors-point

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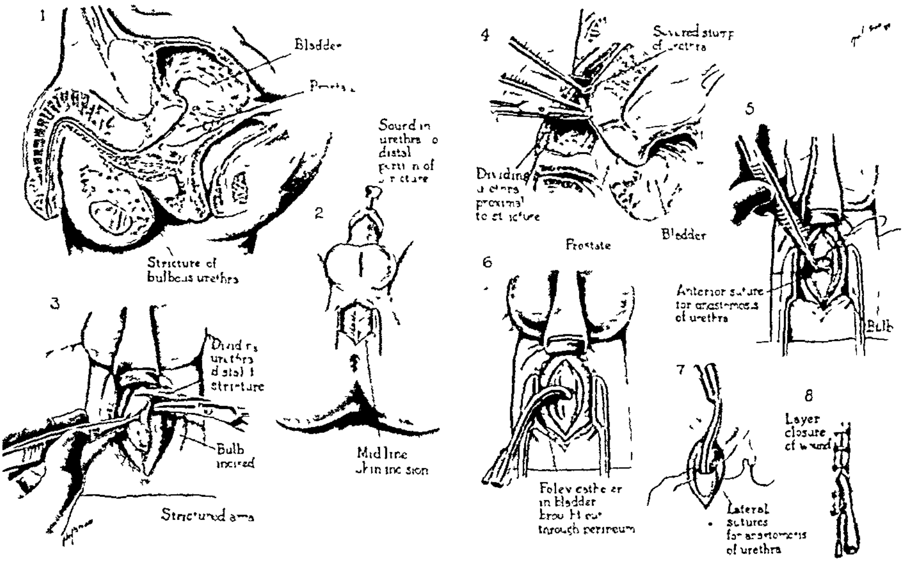
1
Bladder
Prostate
Sound in urethra to distal portion of stricture
2
Stricture of bulbous urethra
3
Dividing urethra distal to stricture
Bulb incised
Strictured area
Midline skin incision
4
Severed stump of urethra
Dividing urethra proximal to stricture
Bladder
5
Prostate
6
Anterior suture for anastomosis of urethra
Bulb
7
8
Layer closure of wound
Foley catheter in bladder brought out through perineum
Lateral sutures for anastomosis of urethra

FIG. 1. *1*, Saggital view showing stricture of bulbous urethra. *2*, Midline skin incision. *3*, Urethra divided distal to stricture as sound is withdrawn. *4*, Saggital view showing division of urethra proximal to stricture. *5*, *6*, *7*, Method of placing sutures for anastomosis. Vesical drainage by catheter brought out through perineum. *8*, Final closure.

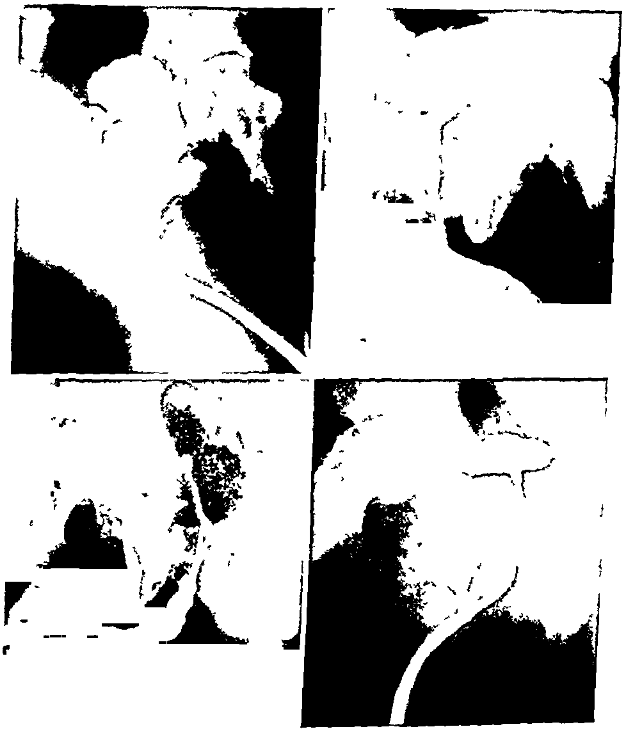

FIG. 2. *A*, preoperative urethrogram. Inflammatory urethral stricture. *B*, six months postoperative. Urethral caliber 26F. *C*, preoperative urethrogram. Elastic inflammatory stricture and pseudodiverticulum. *D*, Six months' postoperative film. Caliber 24F.

and knife-handle dissection, the underlying scar tissue which surrounds the urethra is freed from the muscle. At times it is convenient to section the urethra at the distal extent of the stricture before or during the dissection of the scar from its surrounding structures; but many times the entire strictured portion can be freed as a tubular structure attached at each end to the undiseased urethra. As the posterior extent is reached, a short cuff of proximal urethra is also freed and held with a suture or forceps. Section distal to this suture will then complete the removal of the stricture.

A Foley catheter is then passed through the proximal urethral stump into the bladder, and the bag inflated (fig. 2). The urethral stumps are approximated accurately without tension by 3 or 4 sutures of fine chromic catgut, placed so the knots are outside the urethral lumen. The distal urethral stump can be freed for a short distance to provide enough length to relieve tension; many times this is not necessary. A short midline incision in the ventral aspect of the proximal urethral stump allows the catheter to be brought out through the perineum. Layer wound closure is effected without drainage other than the catheter which acts as a drain to allow the release of serum or blood.

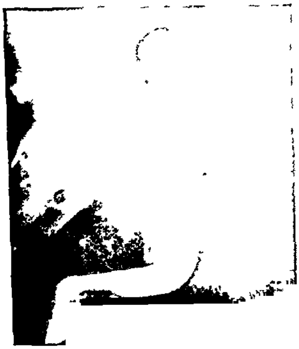

FIG. 3. Ten year follow-up film. Impassable stricture in bulb due to fractured pelvis

If a suprapubic cystostomy has previously been performed, the cystostomy tube is left in place and the urethral anastomosis performed around a catheter introduced per meatum; this catheter is removed immediately after the anastomosis is performed. We feel that the absence of a postoperative urethral splint is of paramount importance in achieving a good end result.

POSTOPERATIVE CARE

No special postoperative care is necessary other than keeping the perineal wound dry and clean. Vesical drainage by either the suprapubic or perineal tube is maintained for ten days at a minimum. Following removal of the suprapubic catheter, a small (16 or 18F) urethral catheter is placed during the period required for closure of the suprapubic fistula. If the operation has been performed without cystostomy, the perineal catheter is removed and no further catheter drainage employed, the wound healing rapidly and urethral voiding becoming established within a few days as a rule.

We have not routinely used chemotherapeutic or antibiotic agents before or during the hospital stay in these patients, but we believe that a strong effort should be made to render the urine sterile following removal of the catheter. In many cases this has happened spontaneously after removal of the obstructing lesion.

RESULTS

The patients are all followed at periodic intervals and the urethral caliber determined by the passage of steel sounds. This is first done 1 month following surgery, and thereafter at intervals of 3 to 6 months for as long as the patient submits to follow-up examination. Urethrography before passage of any instruments has been used in all cases, and a special effort has been made to make a urethrogram at the 6 month follow-up visit (fig. 3).

Complications following this method of treatment of urethral stricture have been conspicuous by their almost complete absence. In a series composed of more than 35 cases of perineal excision we have had no single instance of urinary incontinence, fistula formation, significant infection, or serious hemorrhage. One patient was impotent 6 months following surgery; another, 3 months; both returned to normal sexual potency and have had no further complaints during the following several years. We do, however, regard impotence as a possible sequella following any type of extensive perineal surgery, and this is borne in mind in dealing with the patient in the active sexual age group.

Recurrence of the stricture is of course possible. This has happened in only one instance, and the operator was unable at the time of surgery to remove all of the stricture and still leave enough urethra to anastomose. When symptoms returned, the remaining bit of stricture was resected by the same method, and this patient is now free from symptoms and has a normal urethral caliber. Another patient whose stricture was resected 15 months ago has had some continued residual urine. This patient was felt to have early prostatism and is now awaiting admission for transurethral prostatic resection. The urethral caliber has never been less than 24F in his case. All of the patients have maintained urethral calibers of from 24 to 28F without postoperative dilatation. We do not believe that it is essential that the urethral caliber be 28F; 24 or 26 is adequate, provided the caliber is maintained at this diameter without dilatation. The follow-up period in all the cases has been from 6 months to 10 years.

SUMMARY

A method of operative treatment of certain urethral strictures is presented. Experience with this method of elective resection in 35 cases has yielded gratifying results, and the follow-up has indicated that these urethras remain stricture-free.

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DISCUSSION

DR. A. J. SCHOLL (Los Angeles, Calif.): I want to commend Dr. Maurer and his associates for their results in this large, well handled, series of urethral strictures. Several decades back, radical resection of these fibrous strictured areas was occasionally done. MacGowan, and later Cabot described extensive plastic procedures suitable for certain types of fibrous occluded urethras, but the operation was never popular, done only occasionally and had a very limited field of usefulness. Young stated that he had no experience with such procedures and had never found them necessary.

Urethral injuries and infection are now so effectively treated that strictures rarely occur. Impermeable strictures are only occasionally seen in general hospital clinics and practically never encountered in private practice.

Possibly strictures vary in type and extent in different cities. Several years ago O'Conor reported 8 cases of traumatic stricture which developed from falling astride man hole covers; the man hole covers in Chicago are loose fitting and tip very easily when stepped on. Shortly after this a number of cases of traumatic stricture of the anterior urethra, resulting from forceful twisting, were reported from New York. The strictures I see in California have rarely been difficult to treat. Possibly they grow bigger and develop more fibrous tissue in Kentucky.

Maurer's cases, as he stated, were not relieved or cured by adequate dilatation and needed no after treatment; nevertheless this is quite an extensive operation to do for a condition that usually responds to conservative treatment. During the period, in which fever therapy was the vogue in the treatment of gonorrhea, a number of deaths were reported following that treatment. Keyes in commenting on this subject, said that it was bad enough to have gonorrhea, without dying from it. The treatment of any condition should not leave the patient with a greater trouble than he previously had. Maurer had 2 cases of temporary impotence and I had 1 case of permanent impotence following resection of a stricture. My patient had a severe crushing injury which resulted in an extensive fibrous stricture of the urethra, which I repaired. He recovered, but was permanently impotent. I am quite certain that part of his impotence resulted from his injury, nevertheless I received full credit for his final condition.

Most strictures that are not impermeable will usually respond to dilatation. If it is possible to pass only a filiform, it can be tied in place for 24 hours. Later a small catheter usually can be passed by the obstruction without difficulty and left in the urethra for from several days to a week. This permits drainage and on removal of the catheter it is at times surprising how much the fibrotic area has softened and to what extent the urethra may be dilated.

In one case that responded to dilatation, a stricture was so rigid and so extensive that in attempted dilatation a filiform was broken off at its connection with a small following sound. The bladder was opened and the shaft of the filiform removed, following which another filiform was passed through the urethra. It was replaced the next day by a small catheter. Six days later it was possible to pass a size 26F sound without force. A part of the seeming fibrous thickening not infrequently is due to infection of the peri-urethral tissues and fixation, rest and drainage allow considerable shrinkage and softening of this thickened area.

Dr. Joseph E. Maurer (Louisville, Ky.): I neglected to point out that we use this operation in only 1 or 2 per cent of all cases. We always try dilatation first. Unquestionably, dilatation will serve admirably in a great majority of strictures but, for instance, in the patient who had the diverticulum, dilatation had to be done every three to four days to avoid retention. Before that, the pyuria had never been cleared up, and now the patient's urine is free from pus.

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LUXATION OF THE TESTICLE

DONALD A. CHARNOCK

Luxation of the testicle is the accepted term designating traumatic dislocation of the normally descended organ. The first recorded case was published in 1818.[1] Since this time only sporadic reports have appeared in the literature. In 1929, Alyea made a review of these cases from the year 1800 and brought to light only 23 original reports to which he added two of his own.[2] In 1936, Herbst and Polkey, stimulated by a case entering their clinic, were able to find 93 reports which they considered as falling within this classification.[3] While there is considerable question about accepting all of these cases as true traumatic luxations, the statement that the condition is an exceedingly rare occurrence is attested by their studies.

The testes lie in the scrotum loosely suspended by the spermatic cord and the surrounding fibers of the cremaster muscle. Some support is derived from the intercrural and infundibuliform fascias. The scrotum itself is made up of a thin, easily mobile integument which covers the dartos fibers of unstriped muscle. Contraction of these smooth muscle fibers results from various stimuli. Contractions of the dartos must not be confused with those of the cremaster muscle. The cremaster reflex affects the testicle and not the skin of the scrotum.[4] Direct trauma, sudden violent muscular effort or continued pressure against the testicle may result in its excursion to an abnormal position. The line of migration depends upon the force and direction of the blow, the length of the spermatic cord and the anatomical variations of the pathways along which the testicle progresses.

In view of the increasing incidence of severe pelvic injuries, particularly of the run-over type, it is surprising that this condition is not more frequently encountered. The facility with which the testicles escape injury, due to their mobility and the structure of their covering, has been noted by numerous writers. The protective mechanism of fear and emergency, with its resultant effect upon involuntary muscle fibres, may very well explain nature's effort to protect these vital organs.

Alyea in discussing the course of testicular migration suggests three possible pathways:

1) The internal group in which there is a relaxation of both the neck of the scrotum and of the external inguinal ring. This allows the testicle to be forced into the inguinal canal. There is the possibility of the organ's being forced through the canal into the abdomen and perhaps down into the femoral canal. Several cases have been reported in which the testicle was found within the in-

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 26, 1950.

[1] Claubry, E.: J. gen. med. chir. et phar., Paris, 64: 325, 1818.

[2] Alyea, E. P.: Surg., Gynec. & Obst., 49: 600-616, 1929.

[3] Herbst, R. H. and Polkey, H. J.: Am. J. Surg., 34: 18–33, 1936.

[4] Hinman, F.: Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1935.

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guinal canal. Herbst and Polkey record 2 cases of the migrating organ entering the abdomen. None have been found within the femoral canal. One unusual case reported by Jurinka in 1904[5] describes a run-over accident in which the dislocated testicle was found within the hip joint. See figure 2.

2) The superficial group in which the testicle meets obstruction at the external inguinal ring and does not pass through but is diverted subcutaneously into any position on the circumference of a circle, the hub of which is the external ring and the diameter the length of the cord. In this group we find the superficial inguinal, pubic, perineal, penile, and crural types. These are the more common locations. See figure 2.

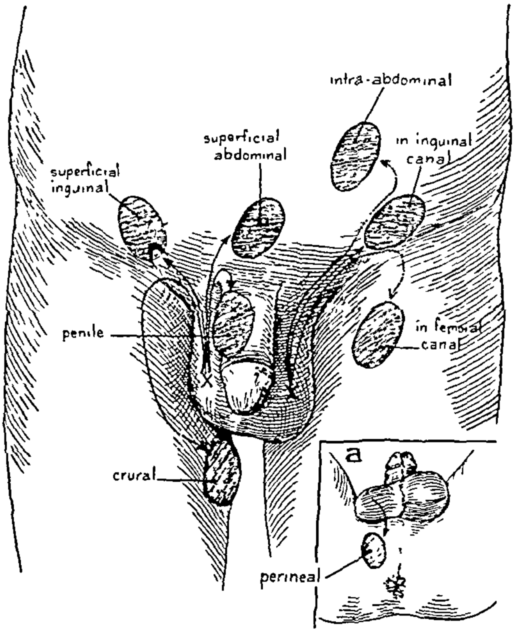

FIG. 1. Pathways of migrating testicle, as outlined by Alyea. Surg., Gynec. & Obst. 49: 600, 1929.

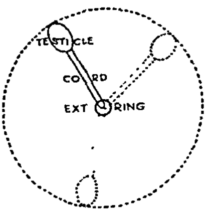

FIG. 2. Diagram of limitations of migration

3) Compound dislocations in which the testicle meets a tight scrotal neck which impedes upward progress resulting in a herniation of the organ through the scrotal wall. A number of these cases have been collected. See figure 3.

Herbst and Polkey have discussed the mechanics of testicular migration and have carried out experimental studies on dogs and human cadaver material. They found no difficulty in causing a migration of the testicle to an abnormal position but stressed the fact that the fascial coverings of the testicle must be injured to result in a permanent fixation in the anomalous location. Their classification of migratory routes corresponded with those of Alyea.

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[5] Jurinka: Zentralbl. f. Chir., 31: 1100, 1904.

Ockuly, in reporting a case of bilateral luxation occurring in a military accident during the recent war, objects to the inclusion of scrotal injuries, with resultant herniation of the testicle through the scrotal wall, within the classification of luxation of the testicle.[6] He believes that this term should be reserved for cases where "a previously normally located testicle assumes a nonscrotal position by being forcibly propelled through normal anatomical apertures or along fascial planes." I believe his point is well taken. In the interests of simplicity the term herniation of the testicle should be used for those cases in which a break in the scrotal wall allows the testicle to lie outside the body.

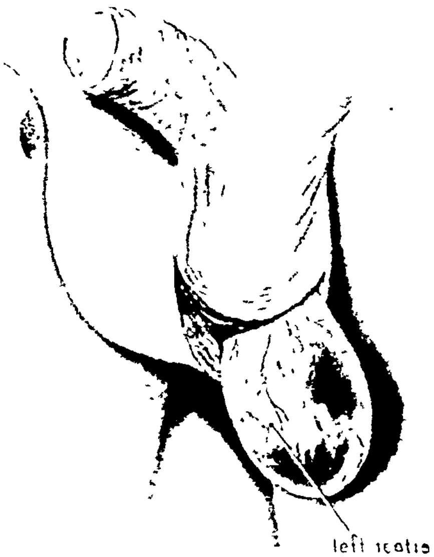

FIG. 3. Hernia of testis. After Alyea

Luxation of the testicle should be limited to: 1) the superficial group, in which the organ is forced to its new location along fascial planes, and, 2) the internal group, where the gland is forced into the inguinal canal and possibly the abdomen.

This condition must at once be differentiated from congenital anatomical anomalies of cryptorchidism and ectopic migrations of the testis. These are present at or develop shortly after birth. Luxation of the testis occurs to a normally descended organ and the change of location is the result of either trauma or muscular effort.

The case to be reported is that of a 40-year-old truck driver who was knocked down and run over by a lumber yard truck. The patient sustained multiple fractures of the right leg and pelvis together with numerous abrasions and severe contusions to the soft tissue over the inguinal canal and thigh. On entry to the hospital it was noted that the right testicle was not present in the scrotum.

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[6] Ockuly, E. A.: Am. J. Surg., 71: 93–95, 1946.

Because of the serious fractures and soft tissue injuries, no further consideration was given to the absent organ.

The patient made an excellent recovery. Numerous skin grafts were necessary to repair the abraded areas. After the dressings were finally removed, the patient, quite naturally, engaged in a personally conducted inventory to establish his physical status quo. He made the distressing discovery that his right testicle was missing from the scrotum. His physician reported to him that on entry to the hospital no testicle was present and that examination had failed to locate the missing organ. Urologic consultation was authorized and a small globular mass was palpated in the area of the midportion of the inguinal canal. This was painful to pressure and was thought to be an undescended right testicle. Palpation of the external inguinal ring was difficult at the time due to the freshly healed tissue. The scrotum was normal in appearance and not atrophic, as is usual in cryptorchidism or congenital ectopic testicle.

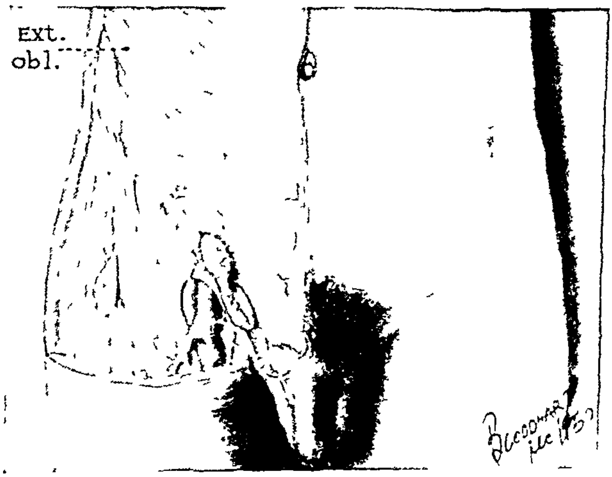

Fig. 4. Superficial inguinal luxation indicating site of testicle as found at surgery

As the patient became more active he complained of pain in the groin on flexing the leg. This was dull and aching in character and increased in severity as the day progressed. It was not referred. There was no abdominal or loin pain. The patient insisted that the testicle was present in the scrotum prior to the accident and in this he was corroborated by his wife. As the discomfort interferred with his rehabilitation, an exploratory operation was authorized by the insurance carrier.

At operation an incision was made parallel to and directly over the inguinal canal. As the subcutaneous tissue was dissected free, the testicle was found lying upon the aponeurosis of the external oblique with the lower pole pointing upward. The tunica vaginalis was intact. The cord was free and entered the external inguinal ring at a rather acute angle. There was no obstruction to the blood supply. The testicle and epididymis were intact. The testicle was slightly reduced in size. It was rather firmly bound to the aponeurosis by a light covering of adhesions. These were easily freed and the testicle and epididymis were re-introduced into the scrotum, which required only manual opening. A Torek fixation was done to insure the testicle remaining in the scrotum. The wound healed rapidly and a month later the Torek flap was released. The patient was discharged as cured.

These cases are rare, but due to an increase in run-over accidents they should be encountered in greater numbers. The diagnostic point to be stressed is the normal empty scrotum. This differentiates the condition from cryptorchidism and ectopic migration of the testis, in which the scrotum is almost invariably atrophic. Diagnosis is frequently hindered by damage to soft tissue, the presence of hematoma, and by edema. In severe accidents the shock and more serious injuries overshadow the abnormal position of the testicle.

Treatment of these cases varies with the length of time between injury and diagnosis. Manual reduction is possible in early cases where edema and injury will allow. When the testicle remains in its abnormal location for a longer time there rapidly develops a covering of adhesions which requires surgical reduction. In the cases recorded these have been highly successful.

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LYMPHANGIOMA OF SPERMATIC CORD: REPORT OF TWO CASES

JOHN K. ORMOND AND ORMOND S. CULP

From the Henry Ford Hospital, Detroit, Mich.

Cysts involving the spermatic cord and scrotal contents may be divided into five groups, according to their origins.

1) Commonest are those rising from the peritoneal prolongation, which include all the true hydroceles. These hydroceles are of several kinds: simple hydrocele of the testis with complete obliteration of the peritoneal extension to the testis; simple hydrocele of the testis and cord, open or closed at the internal ring, involving all or only part of the cord depending on the degree of obliteration; bilocular, with part in the abdominal cavity; and multiple cysts of the cord due to either interrupted areas of obliteration or to inflammatory adhesions. Hydrocele of an old hernia sac is reported but is very uncommon.

2) Cysts of the epididymis. These are of two kinds: retention cysts filled with spermatozoa (spermatoceles), and simple serous cysts.

A spermatocele is a true retention cyst of an aberrant tubule of the rete testis, or, more commonly, of the head of the epididymis, or may arise as the result of obstruction of a tubule which has become distended with semen and dilates. There are two clinical types of spermatocele: intravaginal, occurring between the testis and the epididymis; and extravaginal arising above, and, when large, indistinguishable from hydrocele except by the character of its contents.

Serous cysts may be multiple, are usually small, and are said to arise from the visceral layer of the tunica vaginalis (rarely from the albuginea) and are only important in the differential diagnosis of testicular tumors. Their removal entails removal of the epididymis. Similar to these are cysts arising from the albuginea of the testis proper.

3) Cysts of the foetal remains, müllerian duct and wolffian body: These include the paradidymis or organ of Giraldes, the ducts of Kobelt, the appendix testis and the appendix epididymis. Small cysts of the appendix testis are not uncommon, but the others are rare.

The müllerian duct cysts except for cysts of appendix testis are seen at the prostatic end. The intervening duct is completely obliterated, though theoretically it should be possible for a cyst to arise along its course.

4) Hematoceles, almost invariably due to trauma.

5) Miscellaneous rarer conditions: Echinococcus cysts: filariasis; dermoid cysts; hemangiomas; and lymphangiomas.

We are reporting here 2 cases that belong to the last group. They were remarkable in that their prompt recurrence necessitated another operation less than a month after the first in each case, and their probable nature was not suspected until these recurrences.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 26, 1950.

CASE REPORTS

Case 1. H.F.H., No. 503826, a 2½ year old boy, was seen in urology for the first time on November 28, 1949 at which time the parents claimed that there had been swelling of his scrotum for one year. The patient had been delivered at the Henry Ford Hospital on March 24, 1947, was circumcised before leaving the hospital and had been considered normal. He was admitted with acute tonsillitis from September 14, 1949 to September 16, 1949, at which time the scrotum appeared blue and was approximately 3 times normal size.

He was admitted on the urologic service November 30, 1949. Both testes were palpable deep in the scrotum. The contents on the right seemed entirely normal. The left side was about three times normal size, bluish, and it transilluminated. The swelling extended to the external inguinal ring which was dilated but no actual hernia could be demonstrated. The remainder of the physical examination was essentially negative.

Preoperative diagnosis: Left hydrocele with possible bleeding.

On December 1, 1949 operation was performed by Dr. Culp. The left scrotal contents were exposed through a low inguinal incision under ether anesthesia. The spermatic cord was surrounded by a large amount of fat and numerous small bluish-brown cysts that extended to the external ring and also toward the midline in the presymphyseal area. The inguinal canal was opened, the cord was identified and freed easily and exploration revealed no hernia. The small cysts in the upper scrotum varied from 0.5 to 1.5 cm. in diameter and were excised along with much of the presymphyseal fat on the left side.

The scrotal contents were delivered by combined sharp and blunt dissection and one large cyst about the size of a golf ball was found below the testis and epididymis. It was opened during delivery and proved to be multilocular and very vascular. There was no connection with the testis or epididymis. The tunica vaginalis was opened, the contents appeared normal in every respect and the excess tunica was excised. No attempt was made to explore the depths of the scrotum.

Study of the surgical specimen (No. 110639) showed that the largest cyst weighed 9 gm. The wall was thin, smooth and glistening. Microscopically the wall consisted of heavy collagenous fibrous tissue in which there were many thin-walled veins. The lining consisted of flat mesothelial cells (fig. 1, A).

The postoperative course was uneventful. There was minimal edema on the left side of the scrotum and the patient was discharged on December 8, 1949 (8 days postoperative) with the incision healed.

Five days later (December 13, 1949) he was back in the out patient department with further blue discoloration on the left side of the scrotum. Within the subsequent week it became the size of a hen's egg, fluctuant, and transilluminated. There was no evidence of hernia. The enlargement was confined to the scrotum and no swelling could be found near the symphysis.

He was readmitted on urology on December 27, 1949. Two days later the left side of the scrotum was opened under ether anesthesia. Just under the scrotal skin a large cavity filled with dark bluish-brown fluid was entered. In the depths of this sac the testis was well preserved but adherent. The anatomical arrangement resembled the cavity of a hydrocele of the tunica vaginalis but the tunica had been excised at the previous operation.

The evacuated fluid was centrifuged and the sediment was studied microscopically. It consisted of innumerable red blood cells, a few white blood cells and much fibrin.

The entire sac was excised after which numerous minute, opaque and brownish cysts were found deeper in the scrotum and extending into the perineum. These were embedded in copious fatty tissue. Further dissection included excision of the scrotal septum and all of the cyst-bearing tissue of the perineum. The right tunica vaginalis was exposed but not opened.

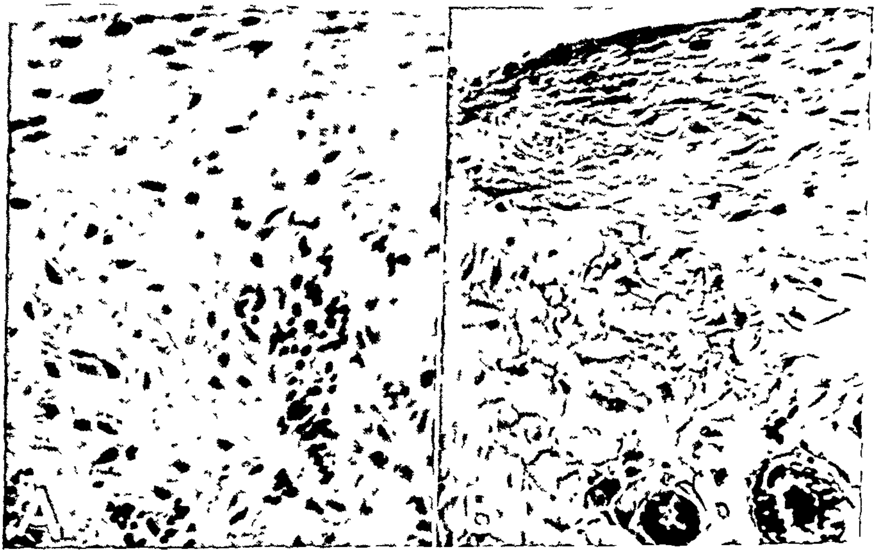

FIG. 1

Histologically (No. 111187) the walls of the cyst showed cellular fibrous tissue in which there were many dilated, thin-walled veins. The linings were not preserved well enough for adequate study.

The convalescence was uneventful and the patient left the hospital on January 4, 1950 (6 days postoperative).

One month later (February 6, 1950) no recurrence had taken place and the child was asymptommatic. The testes were in good position. The right was freely movable, while the left seemed to be fixed to the scrotal wall.

Case 2. H.F.H., No. 512649. The child was not born at the Henry Ford Hospital but had been followed by the department of pediatrics since the age of 3 months for feeding and general care. He was first seen by the division of urology at the age of 28 months at which time it was thought there was a hydrocele of the cord probably communicating with the peritoneal cavity. The parents wished to have this remedied and he was admitted for operation five months later at the age of 33 months. He was a well developed, well nourished child with no abnormalities found in the physical examination except the enlargement in the region of the left cord which was soft and transmitted light. There seemed to be no testicular hydrocele and no hernia could be detected.

Operation was performed by Dr. Ormond on January 7, 1950. Incision was made in the left inguinal region above the inguinal ligament—as for a hernia operation; eventually the external ring was incised and the testicle and cord delivered into the wound. There were found a series of cysts of different sizes running from the gubernaculum to the internal ring. These were incised and dissected out in so far as possible. There was very little fluid under the tunica vaginalis. Also there was no hernia and the cysts did not communicate with the abdominal peritoneum. The testicle was replaced in the scrotum and the wound repaired as in the operation for hernia.

Recovery was uneventful except that on discharge 10 days later, the left side of the scrotum was much enlarged, slightly bluish in color and transmitted light. Previous to operation the scrotum had not been enlarged. There was evidently recurrence of cysts, so he was readmitted to the hospital and a second operation performed on January 24, 1950, seventeen days after the first one.

At this time the left side of the scrotum had increased greatly in size. Incision was made in the scrotum and run up into the inguinal region. There was found to be a cyst bearing, fibrous mass of tissue involving part of the scrotal septum, gubernaculum, tunica vaginalis and running up the cord. In dissecting this cyst bearing tissue from the cord, etc., the corpus cavernosus was exposed near the penoscrotal junction.

Following this operation recovery was uneventful and to date there has been no recurrence.

In neither the tissue removed at the first operation nor in the second, was the lining of the cysts preserved enough for microscopical diagnoses (fig. 1, *B*).

In both of these cases, we have made the diagnosis of lymphangioma, as much on the clinical data as on the microscopic findings, and in this diagnosis Dr. Frank Hartman concurs. These are classed among the rarer conditions, but since the tissue removed at the time of operation for such cysts may be subjected to only perfunctory scrutiny—such tumors may be more common than would appear from a search of the literature.

In Moore's *Textbook of Pathology* it is stated that cystic lymphangiomas occur in the neck and in the inguinal region. Tumors vary from a few small cysts to large masses. On dissection numerous small and large, thin walled cysts filled with a clear straw colored or colorless fluid are seen. Between the cysts there is a small amount of fibrous tissue. Microscopically the cysts are seen to be lined with flattened endothelium which rests upon a moderately collagenous connective tissue. It is highly probable that this tumor originates from some anomaly in the development of the primitive lymphatic spaces. It is commonest in children, on the right rather than on the left and in girls rather than in boys.

A peculiar neoplasm of the serosal layer of the tube and of the epididymis is variously termed lymphangioma, mesothelioma or adenomatoid tumor. (Moore's *Textbook of Pathology*.)

Ewing mentions filariasis of the scrotum but says nothing of lymphangioma.

In *Kaufmann's Pathology*, translated by Reiman, lymphangiomas in general are circumscribed tumors consisting of netlike connected capillary and larger lymph vessels. Cavernous lymphangiomas consist of larger lymph spaces lined with endothelium and surrounded by more or less firm fibromuscular walls. The classic example is macroglossia. Cystic lymphangiomas, or hygromas, consist of cysts, simple and divided, lined with endothelium. The contents are serous, milky or chocolate colored.

Watson and McCarty in 1940 reported on 1056 cases of blood and lymph vessel tumors. In discussing cystic lymphangioma or hygroma, they stated that it may occur in the groin and be multilocular, lined with endothelium and filled with serous fluid. They made the interesting observation that they show a remarkable tendency to recur.

Lymphangiomas are much less common than hemangiomas and are reported in the mesentery, omentum and internal organs such as spleen, liver, intestines, pancreas, broad ligaments, etc., but are most frequent in children in the neck, axilla and groin. In the groin they are oftener found associated with the round ligament in girls, than with the spermatic cord in boys. Treatment has been by radiation, injection of sclerosing fluids, carbon dioxide snow, cauterization and surgical removal. The mortality of those in the neck and tongue has been quite high due to infiltration of the tumor, its remarkable tendency to recur and to extend, and infection. A common complication has been lymphorrhoea.

Those in the groin are apparently much less dangerous and more amenable to surgical removal, which is the usual method of treatment.

REFERENCES

Anderson, W. A. D.: Pathology. St. Louis: C. V. Mosby Co., 1948.

Campbell, M. F.: Hydrocele of tunica vaginalis. Surg., Gynec. & Obst., **45**: 192–200, 1927.

Characke, H.: Lymphangioma of epididymis. Urol. & Cutan. Rev., **43**: 663–664, 1939.

Foged, J.: Lymphangiomata tunicae vaginalis testis. Zentralbl. f. Chir., **66**: 1402–1405, 1939.

Ferris, D. O. and Holmes, C. L.: Extensive lymphangioma of scrotum, penis and adjacent areas. J. Urol., **58**: 453–457, 1947.

Fritzler, K.: Zur Kenntnis der Tumoren des Samenstranges der Schneidenhaute und des Nebenhodens. Ztschr. f. urol. Chir., **18**: 271–277, 1925.

Kaufmann, E.: Pathology for Students and Practitioner. Translated by Reimann. Philadelphia: P. Blakiston's Son & Co., 1929.

Moore, R. A.: Textbook of Pathology. Philadelphia: W. B. Saunders Co., 1945.

Rosenfeld, A.: Case of cystic lymphangioma of spermatic cord. Acta Chir. Scandinav., **59**: 447–454, 1926.

Watson, W. L.: Blood and lymph vessel tumors in children. J. Pediatrics, **15**: 401–407, 1939.

Watson, W. L. and McCarthy, W. D.: Blood and lymph vessel tumors. Report on 1056 cases. Surg., Gynec. & Obst., **71**: 569–588, 1940.

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AN EVALUATION OF TRANSLUMBAR ARTERIOGRAPHY

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Our study of translumbar arteriography was begun approximately 20 months ago using the procedure in selected cases only. As our experience has increased, we have used the technique less specifically and now include it as a diagnostic measure in the study of many conditions. We are attempting to ascertain the diagnostic limits of this type of vascular visualization, especially as applied to urology, and to study any resulting ill effects from this procedure. After performing over 300 translumbar arteriograms, we remain respectful of the procedure, have become enthusiastic about its application in selected cases and have come to appreciate its relative lack of danger. An example of the value of arteriography will illustrate one of the reasons for our above feelings toward this spectacular procedure.

V. W., No. 258063, C. G. H., a 40 year old colored female was seen in the urology clinic in November 1949, for urethral dilatations because of stenosing fibrotic lymphopathia venereum. At a routine return visit on January 2, 1950, the patient complained of a throbbing pain in the left costovertebral angle of 4 days' duration. There were no new urological symptoms. Retrograde pyelograms, taken the next day, revealed a space-consuming lesion in the lower pole of the left kidney (fig. 1,*A*). Urinalysis of ureteral specimens was normal. Divided phenolsulfonphthalein excretion was normal. Our diagnosis, of necessity, was a mass encroaching upon the left renal pelvis—tumor vs. cyst. An arteriogram (fig. 1,*B*) revealed an avascular area in the region of the mass in the left kidney. The avascularity was consistent with the diagnosis of renal cyst. Surgical exploration of the left kidney for correlation of the arteriogram and pathological state confirmed the diagnosis of solitary renal cyst.

The full application of the values of translumbar arteriography is still unknown. We believe that it will, with time and in selected cases, become as important to urologists as most of our now routine procedures.

Vascular visualization with contrast media was accomplished within a short time after Roentgen announced his epoch-making discovery in 1895. Haschek and Lindenthal visualized peripheral vessels in an amputated arm at that time, but the contrast medium used was not applicable to clinical use because of its toxicity. Cameron, in 1918, discovered that the iodide molecule was radio-opaque. This, in addition to Rowntree's disclosure that the renal parenchyma possessed the ability of selective secretion and concentration of the salts of iodides, opened an entirely new field of diagnostic possibilities to the urologist; namely, excretory and retrograde urography as well as vascular visualization. However, it was not until 1924 that Barney Brooks began peripheral vessel visualization as a diag-

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Read at annual meeting, American Urological Association, Washington, D. C., May 30, 1950

A sequel to this paper will appear in the July issue. *Editor* nostic aid. It was a Portuguese urologist, Dos Santos, who first realized and visualized the application of arteriography by the translumbar route of the abdominal aorta as an aid to the urologist. He reported the technique and the value of this procedure to the Surgical Society of Paris in 1929. Dos Santos came to the United States in the early 1930's and demonstrated the technique and presented his findings before a number of urological and surgical groups. Among others, O. A. Nelson of Seattle and A. Keller Doss of Ft. Worth viewed Dos Santos' demonstration and realized the values of this diagnostic procedure. Apparently they possessed less temerity than other American urologists for when the opportunity presented itself, they punctured the aorta to produce arteriograms. These two men in 1942 independently, but almost simultaneously, published reports of their experiences with translumbar arteriography and thereby pioneered this procedure in the United States.

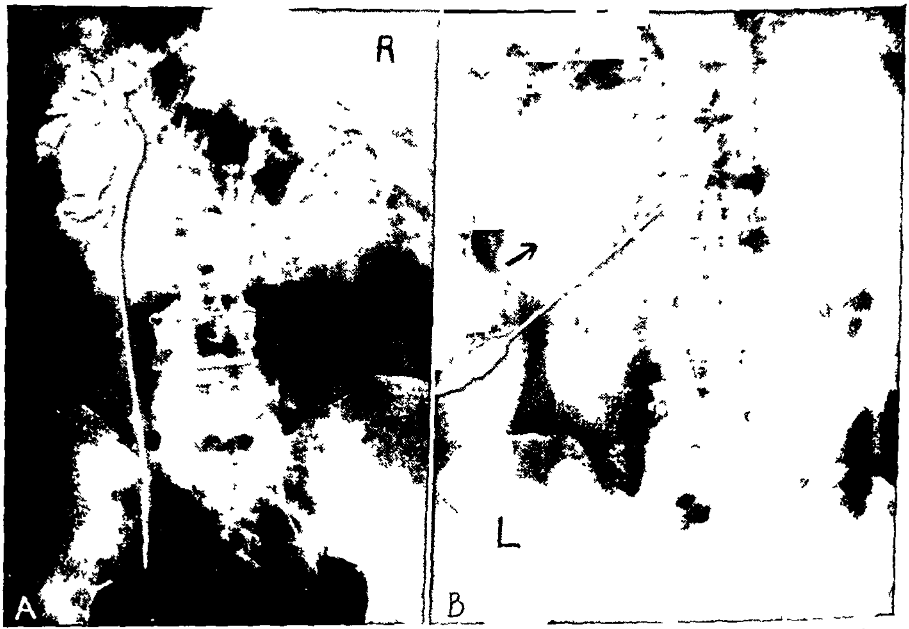

FIG. 1. *A*, mass encroaching upon left renal pelvis *B*, avascular area in region of mass, indicating cyst.

Our initial interest in this study was prompted by a suggestion of one of us that this diagnostic technique might satisfy our desire to study the vascular system of the kidneys in certain individuals complaining of pain, obviously renal-like in nature, in whom ordinary urologic diagnostic methods had failed to reveal evidence of abnormality of the kidney.

It has long been known that the cause of renal pain is an increased intracapsular pressure. Any interference with the mechanical efficiency of either of the two exists from the renal parenchyma, ureter or vein, predisposes to the development of an increased pressure within the thin and relatively inelastic renal capsule. It is also logical to state that the completeness of this interference and the rapidity of its development directly control the severity and the acuteness of the resulting attack of renal pain.

Ureteral catheterization and excretory and retrograde pyelography have made it possible for us to thoroughly investigate the mechanical efficiency of one of these exits from the renal parenchyma. We hope that the continued development of translumbar arteriography and the more accurate interpretation of arteriograms will allow us to form as satisfactory an estimate of the efficiency of the venous exit from the kidney parenchyma as we are now able to obtain of the urinary exit. We have made some progress in this direction, but an unbiased appraisal of the experiences of many observers will be necessary before present day assumptions become facts.

EQUIPMENT

The equipment for arteriography of the abdominal aorta, which we now use, is extremely simple. It requires little space, a fact of importance in the usually small x-ray room, is easily transported from one hospital to another, is not cumbersome, confusing or distracting to the operator, for it is simply the equipment essential to the performance of the procedure itself. The equipment consists of a tray draped with a sterile sheet, a medicine glass, a 10 cc Sana-Lok control syringe, an adapter for the syringe and one for the needle with plastic tubing attached to each adapter, four sterile towels for draping the patient, a 6 inch, 18 gauge needle for the puncture, as well as sterile gauze for the surgical-like scrub of the lumbar area.

TECHNIQUE OF PROCEDURE

A scout film of the lower chest, abdomen and pelvis is made with the patient in the prone position on the x-ray table. The film is exposed at 0.10 of a second which requires a high-speed Bucky diaphragm. The patient's back is then given a surgical-like scrub and the left lumbar area draped with sterile towels. The scout film is reviewed and any adjustment in exposure technique or position of the patient is made. The patient is anesthetized with intravenous sodium pentothal in a hand or wrist vein. An 18 gauge, 6 inch needle is then inserted at the lower edge of the twelfth rib, 8 cm. to the left of the spinous processes, in the average-sized adult. The needle is passed superiorly, ventrally and medially to the body of the eleventh or twelfth thoracic vertebra, no lower. Then, in gradual step-like fashion, the needle is advanced ventrally along the body of the vertebra by slight withdrawal of the needle and re-insertion. The needle is finally passed just under the anterior left edge of the proper vertebra. The stylet is then removed and the needle advanced ½ to 1 cm. at which point it enters the aorta with a sudden release of the resistance as if entering the subarachnoid space when performing a spinal puncture. The 10 cc Sana-Lok control syringe with plastic tubing, which has previously been filled with contrast medium, is then attached to the needle. It is imperative that there be retrograde flow of blood into the plastic tubing and pulsation of this column of blood before injection is made. The rotary anodes of the x-ray machine are started in motion and the 12 cc solution is injected in 1½ to 2½ seconds. The film is exposed as the last cubic centimeter is injected. The needle is immediately withdrawn and a second film is promptly taken to obtain a nephrogram. The entire procedure from the start of the anesthesia requires approximately 3 minutes. If there is a failure, repeat arteriograms are not made within 24 hours but we do not hesitate to return the patient to the x-ray department, repuncture the aorta and repeat the injection of the contrast medium the following day.

We have used 75 per cent neo-iopax and 70 per cent diodrast and are now studying the values of 70 per cent urokon.

COMPLICATIONS OF PROCEDURE

We have been asked, "Why is there so little translumbar arteriography being performed in this country?" To us the answer is quite clear; there is an apparent but unjustified fear of puncturing the aorta with a needle. We, too, were concerned when we first utilized this procedure; however, in over 300 cases of aortic puncture, we have had no fatalities and the morbidity has been amazingly insignificant. Our patients, routinely, are ambulatory and partaking of a regular diet within 2 to 3 hours after completion of the study. The only complaints made by our patients have been those of occasional lower left chest pain and infrequently, left shoulder pain.

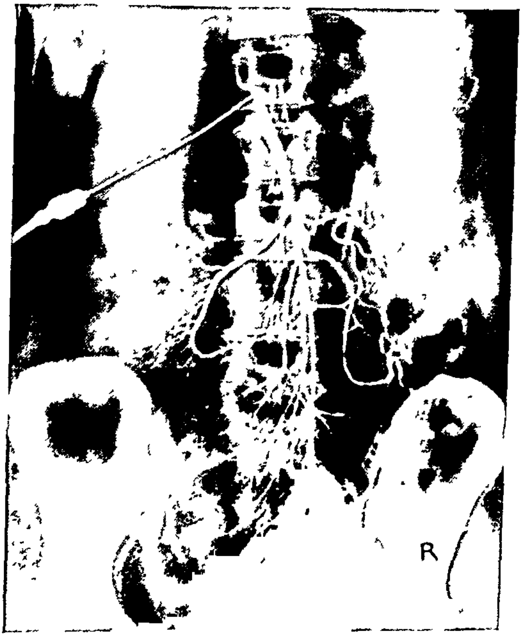

FIG. 2. Injection of superior mesenteric artery; note colonogram

Mesenteric thrombosis with resulting death has been reported following the injection of contrast medium into the superior mesenteric artery. We have accidentally injected solely the superior mesenteric artery on several occasions without ill effects (fig. 2). Accidental superior mesenteric artery injection of contrast medium results in mesenteric thrombosis because of one or a combination of the following: 1) use of too great a quantity of contrast medium, 2) too great an injection pressure, or 3) the use of too toxic and irritating a contrast medium. Any one or combination of the before-mentioned may produce excessive end artery spasm with resulting ischemia and thrombosis. The injection of a less irritating contrast medium and injection of contrast medium in less quantity per second will aid in preventing this accident should the mesenteric artery be injected accidentally. The best means of prevention of this accident is injection of the aorta at T-11 or T-12 vertebra, which is always above the coeliac axis.

The performance of translumbar arteriography has not been utilized by many physicians because of fear of hemorrhage following aortic puncture. This possible accident was of concern to us when we began our study of this diagnostic tool, but as our study has progressed it is apparent that this fear is unwarranted.

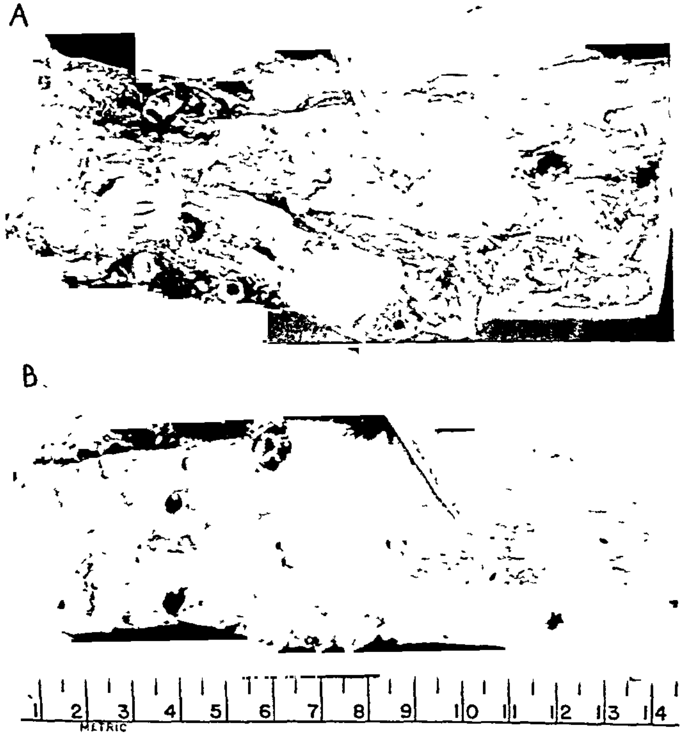

FIG. 3. *A*, location of aortic puncture in peri-aortic tissue of patient with hypertension. Note absence of bleeding. *B*, clean puncture of aorta through atheromatous plaque.

In order to determine the effect of aortic puncture by an 18 gauge needle, we have made two types of studies, one in which we have in 13 moribund patients purposely punctured the aorta before death (30 minutes to 4 days) and have studied the aortas of these patients at the autopsy table; in a second group, we have made studies of the aortas of 9 patients upon whom aortic punctures were performed and who succumbed 24 days to 6 months after puncture, from causes other than the aortic puncture.

In the first group, 11 of the 13 patients had no evidence of extra-aortic bleeding (fig. 3, *A*) in spite of the fact that 7 of them had hypertension with a diastolic pressure greater than 110 mm. of Hg. The remaining 2 patients had small (1–2 cm.) areas of hemorrhage at the puncture site with no evidence of fresh bleeding. The aorta, in no case, showed evidence of a large tear and in all, it was quite difficult to locate the site of puncture (fig. 3, *B*). In 2 cases the puncture was through an atheromatous plaque, yet no evidence of hemorrhage was seen.

In the second group of 9 patients, we could find no abnormalities of the aorta or peri-aortic tissue. We have punctured the aortas of patients with diastolic pressures of over 140 mm. of Hg. without apparent ill effect. On several occasions, puncture of a sclerotic aorta has been recognized by the grating sensation of a calcareous plaque against the needle (fig. 4) yet no ill effects resulted. Some patients who have aortic puncture may bleed a small, but not dangerous, amount. This bleeding we consider to be similar to, but of no more clinical importance than the bleeding seen following venipuncture. We do not consider hypertension or arteriosclerosis a contraindication to the procedure. Any patient who is physically suitable for sodium pentothal anesthesia we consider to be a candidate for translumbar arteriography, unless the patient is sensitive to iodides or is in renal failure. None of the patients in our series of translumbar aortic punctures has suffered ill effects from the procedure.

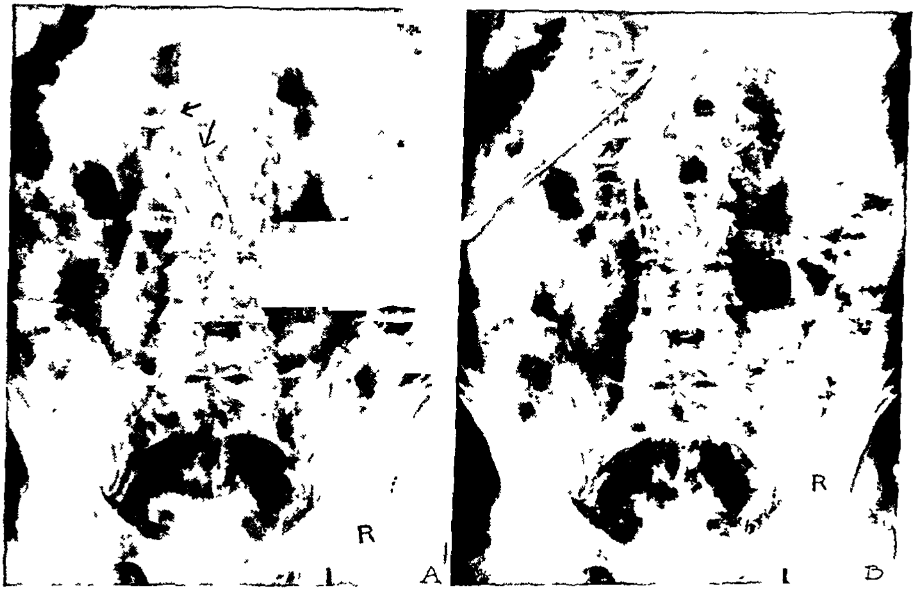

FIG. 4 *A*, sclerotic aorta and calcification in region of non-functioning left kidney. *B*, contrast medium filling sclerotic aorta and demonstrating sclerotic plaque obstructing left renal artery.

Aortic intramural injection of contrast medium has not been previously reported. When encountered by us, considerable speculation and concern resulted (fig. 5). The possibility of necrosis of the aortic wall, with rupture, was discussed. We have seen only one patient in whom contrast medium appeared to be injected into the wall of the aorta. This patient expired 24 days later due to cardiac failure from arteriosclerotic hypertensive heart disease, and at autopsy the aortic wall and peri-aortic area were without abnormality (fig. 6).

Extra-aortic injection of contrast medium, or extravasation of it, has been of concern to all when first seen. This has occurred more than 25 times in our series. The amount of contrast medium injected outside the aorta has varied from a few cubic centimeters to the entire contents of the syringe, 12 cc. In all of these cases, follow-up films, when made, reveal complete absorption of the contrast medium just as one observes in intramuscular injection of contrast medium for excretory urography in children. These patients are, of course, predisposed to pain in the area of the lower left chest but otherwise have no difficulties. We have made no attempt to aspirate or surgically drain the area of extra-aortic injection nor have we considered it necessary.

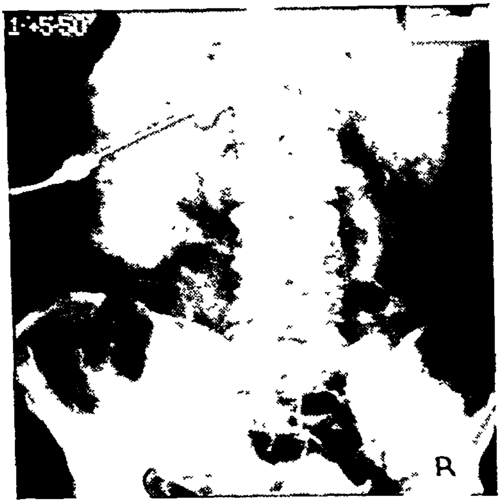

Fig. 5. Case E. M. Aortic intramural injection of contrast medium

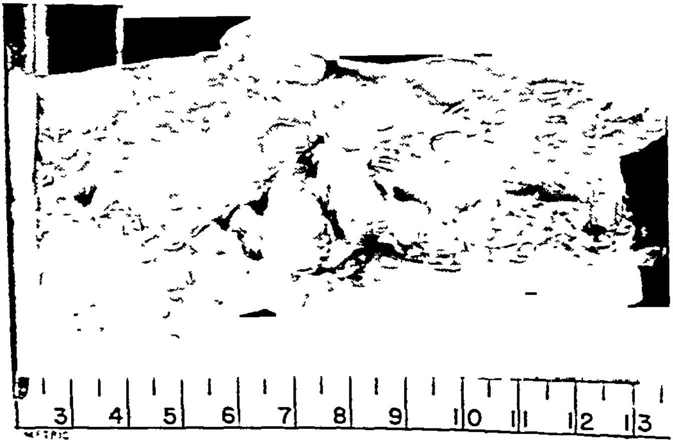

Fig 6. Case E. M. Aorta and peri-aortic tissue without abnormality 24 days later at autopsy.

The use of sodium pentothal anesthesia, with the patient prone, is not ideal.

Patients receiving sodium pentothal are apt to develop laryngeal spasm, although preoperative atropine medication makes it less likely. The patient in the prone position with laryngeal spasm is most difficult for the anesthetist to manage. However, should laryngeal spasm occur, the procedure can be interrupted in several seconds by promptly removing the needle and quickly turning the patient to the supine position for proper care by the anesthetist.

Sensitivity to the contrast medium has not been seen by us. We require that all patients have an excretory urogram made with the contrast medium being used for arteriography at least 24 hours before arteriography is performed or have an intravenous test of sensitivity to ¼ cc of the contrast medium before aortic injection. In addition, it is imperative to ascertain that the patient is not in renal failure.

Acute iodinism has not been seen in our series because we use a quantity of iodide that is very little greater than that normally used for excretory urography. Acute iodinism was reported by Nelson and an attempt made to prevent it by immediate post-arteriogram therapy with 1000 cc intravenous sodium chloride and ascorbic acid. We originally used this therapy but discarded it early in our studies as we believed that it is unnecessary when only 12 cc contrast medium is injected.

The perforation of an intraperitoneal hollow viscus with the needle while attempting aortic puncture has most certainly occurred, but has not been recognized, in our series. We do not believe that this is a dangerous event. We are certain that intraperitoneal hollow visci may be perforated by a needle without gross contamination of the peritoneal cavity and without continuous leakage of the contents of the hollow viscus. It is certainly an event to be avoided, if at all possible.

Pneumothorax can occur due to 1) abnormality of position of the pleura, or 2) carelessness or confusion on the part of the operator. When it occurs, it may easily be treated by simple aspiration of the pleural space with the puncture needle and a syringe. We have not seen this accident in our series.

It is our belief that the dangers of arteriography are amazingly limited and that such dangers as do exist, result from carelessness and haste on the part of the operator. In instructing our assistants in the technique of performing translumbar arteriography, it has become increasingly evident that although the technique is simple, absolute precision is necessary. We have found that haste and "short cuts" lead to poor results, anxiety and disappointments.

VALUES OF ARTERIOGRAPHY

The vascular pattern of the renal parenchyma in the normal state is typical. Abnormalities of the renal parenchymal arterial pattern are therefore important; the number of arteries entering the renal mass and the point of their entrance are often significant. We have found arteriography to be of value to the urologist in the following ways:

1) to demonstrate aberrant vessels to the kidney in normal position;

2) demonstrate anomalous vessels to the abnormally-located kidney (fig. 7); 3) to visualize the presence of renal blood supply and renal mass as seen by the arteriogram and nephrogram of patients in whom the character of the renal mass is otherwise undetectable due to ureteral obstruction and a nonfunctioning kidney;

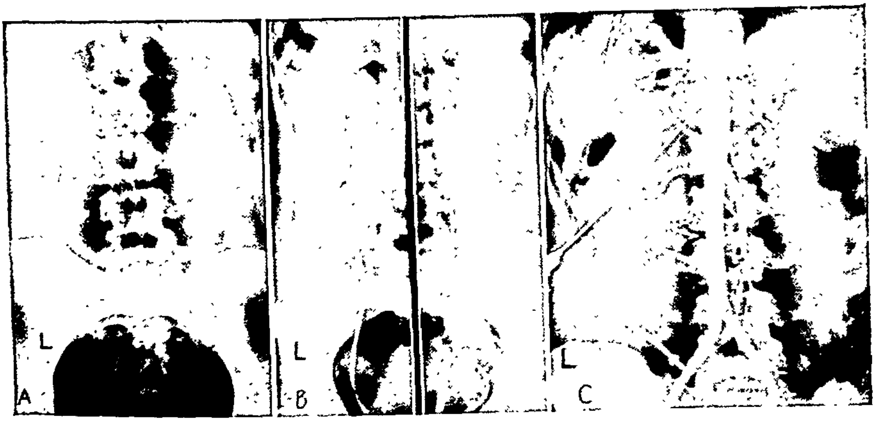

FIG. 7. *A*, nonfunctioning right kidney by excretory urography; abnormal appearing left kidney. *B*, hypoplastic right kidney and non-rotated left renal mass. *C*, minimal right renal blood supply. Anomalous left renal arteries—3 from aorta and one from common iliac artery.

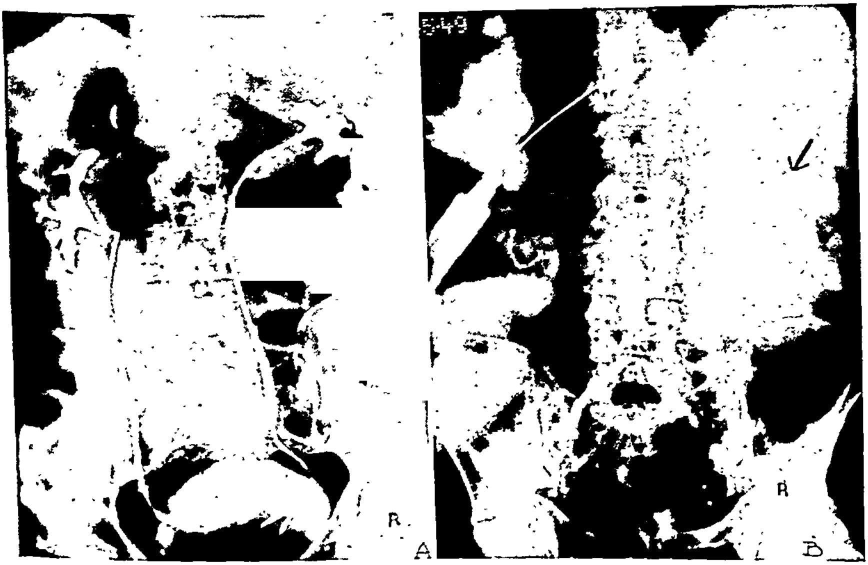

FIG. 8. *A*, mass encroaching upon right renal pelvis. *B*, pooling, puddling and laking of contrast medium in right renal mass, pathognomonic of tumor, proven at surgery.

4) to demonstrate that the potential function of a kidney is in direct relationship to the quantity of the blood supply of that organ;

Patients receiving sodium pentothal are apt to develop laryngeal spasm, although preoperative atropine medication makes it less likely. The patient in the prone position with laryngeal spasm is most difficult for the anesthetist to manage. However, should laryngeal spasm occur, the procedure can be interrupted in several seconds by promptly removing the needle and quickly turning the patient to the supine position for proper care by the anesthetist.

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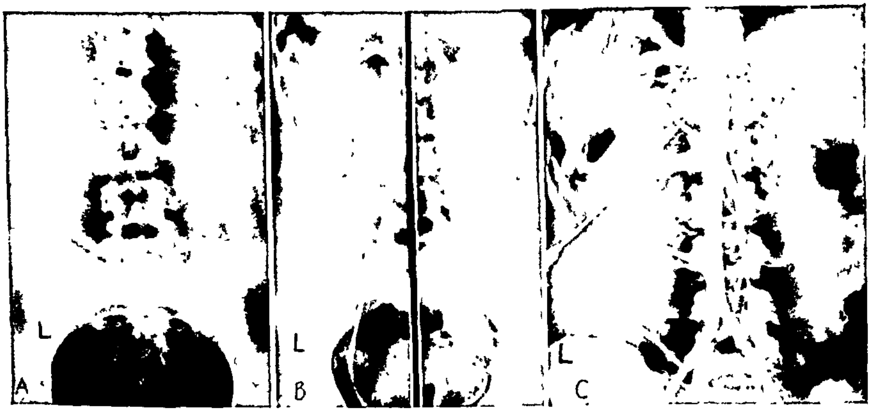

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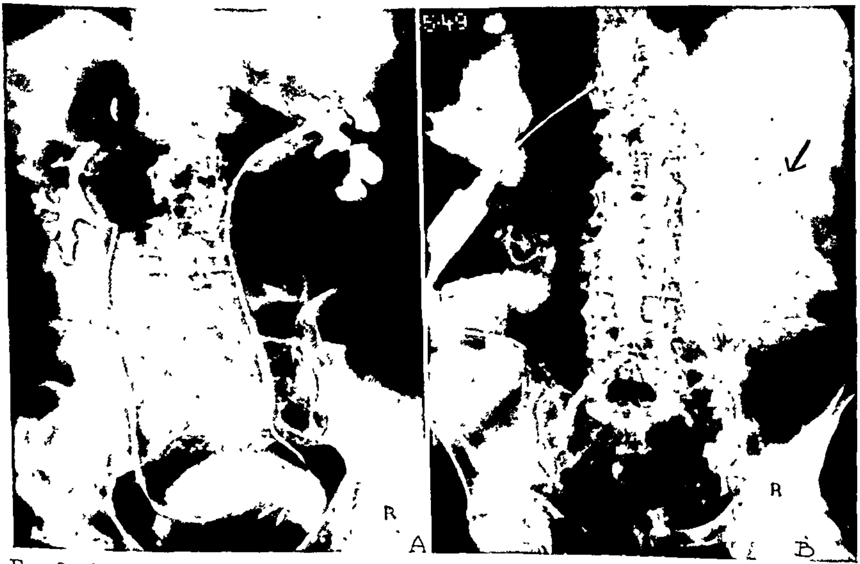

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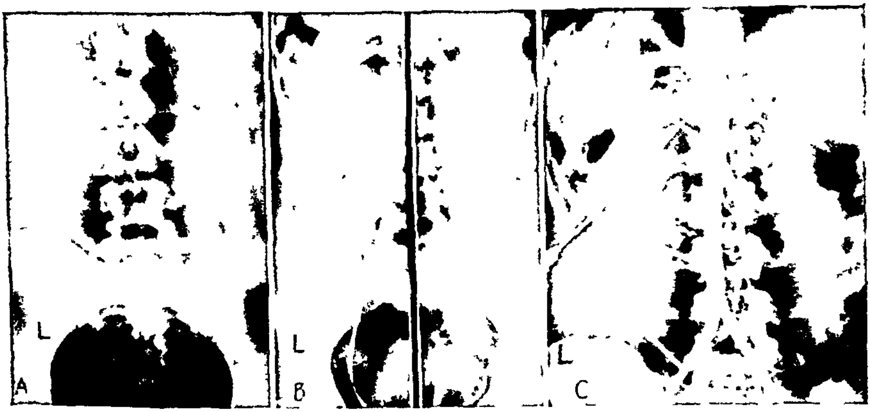

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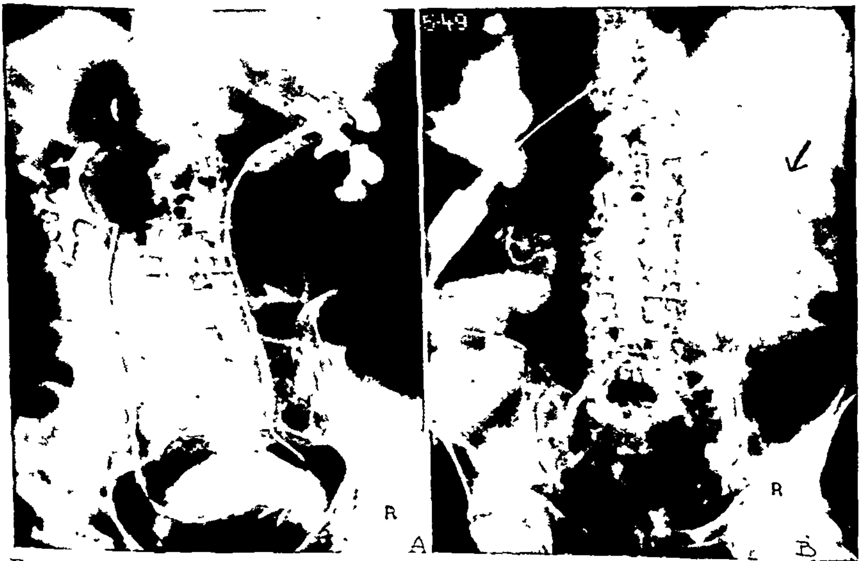

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4) to demonstrate that the potential function of a kidney is in direct relationship to the quantity of the blood supply of that organ;

5) to reveal that avascularity of an area of a kidney, in which there is a space-consuming lesion, indicates cyst (figs. 1, *A* and *B*);

6) to confirm that laking, puddling and pooling of contrast medium in the area of a renal space-consuming lesion is pathognomonic of tumor (fig. 8);

7) to differentiate aneurysm of the splenic artery, aorta or other abdominal arteries from other intra-abdominal masses and calcifications;

8) to demonstrate renal artery or even aortic obstruction (fig. 4);

9) to differentiate extrarenal retroperitoneal tumors from renal tumors; and

10) to evaluate the renal blood supply of hypertensive patients to determine if the Goldblatt phenomenon is in effect.

Although we now rely upon the information obtained from translumbar arteriography in upper urinary tract studies, we remain cognizant that improvement of certain aspects of this procedure will increase the scope of its usefulness.

We believe that a more opaque contrast medium is necessary. One obtains adequate concentration of the contrast medium in persons whose weight is less than 180 pounds, if they are not too obese, but when the torso mass becomes great, a more opaque contrast medium is desirable.

We are aware of a lack of experience in interpreting arteriograms. There is a great need for further correlation of arteriograms and pathological material, as well as joint study and interpretation of films by separate groups. The interpretation of renal arteriograms is at much the same point as pyelographic interpretation was 5 years after its inception.

Translumbar arteriography of the abdominal aorta requires a general anesthetic. We have never made arteriograms under local anesthesia, although it could possibly be accomplished by procaine flooding of the area of aortic puncture. However, the insertion of the needle to that depth under minimal anesthesia would be quite traumatic and immobility of the patient while the needle is in the aorta is considered imperative. Spinal anesthesia has been used in our series and it is satisfactory; however, the anesthetic level must be high and the anesthetic persists too long a time for a simple 3 minute procedure.

We have attempted aortic puncture on 5 children under 9 years of age. In all, the puncture has not been accomplished, probably because of failure of the aorta to lie to the left side of the vertebral bodies in the region of T-10—L-2.

Utilization of multiple film exposures during the injection of contrast medium is an addition to the presented technique that will undoubtedly give further valuable information. We have used this new method in a portion of our series. A more detailed report will follow evaluating the Fairchild multiple film exposure procedure.

SUMMARY

It is our impression that translumbar arteriography of the abdominal aorta meets the criteria for a perfect diagnostic procedure in that 1) it is relatively safe, 2) the degree of skill demanded can be acquired with relative ease, 3) the procedure satisfies the physician's curiosity in his differential diagnostic program, 4) the procedure is often of definite value in making a diagnosis, 5) the

procedure frequently aids in the estimation of the prognosis, and 6) the procedure frequently enables the physician to make a more intelligent decision as to the proper method of therapy. It is our belief that it is important that all urologists equip themselves with the knowledge of translumbar arteriography of the abdominal aorta, for it can be of great value in completing the diagnostic study of selected urological and associated cases.

1908 Union Central Bldg., Cincinnati, O.

REFERENCES

Brooks, B.: Intra-arterial injection of sodium iodid. J. A. M. A., **82:** 1016–1019, 1924.

Cameron, D. F.: Aqueous solutions of potassium and sodium iodids as opaque mediums in roentgenography. J. A. M. A., **70:** 754–755, 1918.

Dos Santos, R., Lamas, C. and Caldas, P.: Recent progress in the technique of arteriography of the abdominal aorta. Presse med., **39:** 574–577, 1931.

Doss, A. K., Thomas, H. C. and Bond, T. B.: Renal arteriography, its clinical value. Texas State J. Med., **38:** 277–280, 1942.

Doss, A. K.: Renal hypertension: The value of translumbar arteriography in its diagnosis. A preliminary report. Texas State J. Med., **39:** 188–194, 1943.

Doss, A. K.: Translumbar aortography: An apparatus for injecting the radiopaque media. Surgery, **16:** 422–424, 1944.

Doss, A. K.: Translumbar aortagraphy: Its diagnostic value in urology. J. Urol., **55:** 594–606, 1946.

Doss, A. K.: The management of ureteropelvic juncture obstruction: Translumbar aortagraphy an adjunct. J. Urol., **57:** 521–538, 1947.

Evans, A. T.: Translumbar aortagraphy: A preliminary report. Cincinnati Med. J., **32:** 47–56, 1951.

Hartnett, L. J.: Visualization of the maternal circulation at the site of the placenta (placentagrams). J. Missouri State M. A., **44:** 754–756, 1947.

Haschek, E. and Lindenthal, O. T.: Ein Beitrag zur praktischen Verwerthung der Photographie nach Rontgen, Wein klin. Wchnschr., **9:** 63–64, 1896.

Henline, R. B. and Moore, S. W.: Renal arteriography: Preliminary report of experimental study. Am. J. Surg., **32:** 222–229, 1936.

Nelson, O. A.: Arteriography of abdominal organs by aortic injection: A preliminary report. Surg., Gynec. & Obst., **74:** 655–662, 1942.

Nelson, O. A.: Arteriography in renal and abdominal conditions. J. Urol., **53:** 521, 1945.

Osario, P. A.: Abdominal aortography. J. A. M. A., **100:** 1555, 1933.

Osborne, E. D., Sutherland, C. G., Scholl, A. J. and Rowntree, L. G.: Roentgenography of urinary tract during excretion of sodium iodide. J. A. M. A., **80:** 368–373, 1923.

Price, A. H. and Wagner, F. B., Jr.: Complete occlusion of the abdominal aorta: Report of two patients diagnosed by aortography. Surg., Gynec. & Obst., **84:** 619–624, 1947.

Röntgen, W. C.: Uber eine neue Art von Strahlen, S. B. d. phy-med. Ges zu Wurzb. pp. 132–141, 1895.

Witt, A. E. and Melick, W. F.: Studies on translumbar aortography: A simple apparatus for translumbar aorteriography. J. Missouri State M. A., **44:** 749–754, 1947.

Wagner, F. B., Jr.: Complications following arteriography of peripheral vessels. J. A. M. A., **125:** 958–961, 1944.

Wagner, F. B., Jr.: Arteriography in renal diagnosis: Preliminary report and critical evaluation. J. Urol., **56:** 625–635, 1946.

Wagner, F. B., Jr., Price, A. H. and Swenson, P. C.: Abdominal arteriography: technique and diagnostic application. Am. J. Roentgenol., **58:** 591–598, 1947.

Wagner, F. B., Jr., and Price, A. H.: Fatality after abdominal arteriography. Surgery, **27:** 621–626, April, 1950.

DISCUSSION

Dr. A. Keller Doss (Fort Worth, Texas): It is gratifying to those of us who have been interested in this procedure for a time to see that Doctors Smith, Rush and Evans have won a first prize for their excellent exhibit presented at this meeting. Well do I remember that an exhibit presented at Cincinnati 4 years ago was viewed by many as both foolish and fantastic, a mere medical curiosity.

Translumbar aortography remains a procedure not to be turned over to one's resident to be developed in off hours. Adequate time and preparation in an effort to acquaint oneself with the various problems incidental to its execution are still worth while.

Translumbar aortography in no way replaces the various methods which have been commonly used to investigate the upper urinary tract. It does, however, serve to strengthen immeasurably the foundation on which sound diagnostic measures rest. Arteriography afforts an entire new approach in the study of pathology and deranged physiology. By study of the architectural pattern of vessels and a correlation of them with careful pathological study, we now are able further to push back the frontier of diagnostic urology.

The full benefit to be derived from the procedure awaits, as it has since its first introduction by dos Santos in the late twenties, the development of an innocuous contrast medium capable of producing fine visual detail upon injection of small amounts of the solution, and the general availability of movie roentgenographic apparatus which can record continuous progress of the solution throughout the vascular tree. The latter is now available to some. The medium remains undeveloped.

As yet, translumbar aortography seems to offer most to the genito-urinary surgeon in its ability to assist in the conservation of renal parenchyma. Given another 10 years and this procedure will be rather generally adopted.

Dr. O. A. Nelson (Seattle, Wash.): Doctors Smith, Rush and Evans have given us an excellent exposition on arteriography. They have elaborated well on the hazards and complications of the procedure.

In a recent European trip, I found arteriography used rather frequently. At the American Hospital in Paris, they told me that they do sometimes up to eight arteriograms in one week. That is, of the abdominal organs and extremities. The operator put two needles in the aorta; then injected two streams of the opaque medium. Doctor Weyde, a radiologist in Oslo, is doing some good work in arteriography. Doctor Semb uses arteriography to determine the feasibility of partial nephrectomy for tuberculosis. Although he utilizes ureteral catheterization and pyelography, arteriography is used to determine the location of the lesion and the blood supply in the kidney.

Doctor Lindblom, a radiographist in Stockholm, not only uses arteriography, but has worked out a rather detailed method of injecting the kidney itself with opaque medium. A week ago today, I saw him inject a kidney that contained multiple cysts. The procedure is as follows: With a patient resting on his side, the kidney to be examined in the upward position, he injects an excretory urographic substance and places a graduated metal bar from the lower portion of the chest to the iliac crest. Then, after measuring the distance on the films made to the kidney area, he does fluoroscopy and determines the location where the point of the needle is to be placed. The skin is then rendered sterile, injected with novocaine, and a needle passed down to the desired area. As he advances the needle in the kidney substance by a syringe, he asperates as he advances. If he obtains fluid from the kidney substance other than from the pelvis, he knows he's dealing with a cyst or cysts. If he obtains blood, it usually means that he is dealing with a vascular tumor. Then, he injects a very small amount of opaque medium. He may have to make several punctures and several urograms before coming to a conclusion as to the diagnosis.

In Oslo, I was told of a patient who developed paraplegia following translumbar arteriography. I did not have a chance to interview the physician who made the injection. However, he used one of the intravenous pylographic substances of 70 per cent. We shall probably never know just what happened, but know that, in certain types of backs, the needle might inadvertently be passed into the spinal canal. Consequently, a needle entering the spinal cord at such a high location might conceivably have injured the spinal cord.

To point out the advantage of arteriography when clinical signs and symptoms suggest the presence of a pheochromocytoma, I wish to show a slide of a patient with such a tumor located at the lower pole of the right kidney. I would suggest that, before doing arteriography or any other procedure on such a patient, the blood pressure should first be stabilized by benodaine hydrochloride or an adrenolytic drug. Finally, although arteriography has a rather limited indication in the diagnostic field, certain information may be obtained by this procedure that cannot be determined by any other diagnostic method.

Dr. Arthur T. Evans (Cincinnati, Ohio): We have performed a lot of arteriograms and we have not done them always for specific reasons. We believe that it is only by doing repeated translumbar arteriograms that we will be able to perfect a technique, improve our interpretation of arteriograms and accumulate a large enough series to truly evaluate the morbidity and the mortality from the procedure. It is not a procedure to be undertaken lightly. It is a procedure that we still undertake with a certain amount of care. We supervise any of our assistants who do the procedure. As a result, we have shown, I think, with the lack of any deaths in our series of 300, that the mortality rate is not high enough to make the procedure prohibitive because of its accompanying danger.

I do want to add this last note. I am certain that no investigator in this field knows a great deal about translumbar arteriography. I believe that Doctor Nelson and Doctor Doss will agree with us. We have seen only a very, very few arteriograms, when compared with the number of pyelograms that you and I have seen. If one of our assistants has seen only 300 pyelograms, he has not seen many and his interpretation is wanting in experience. That is exactly the way we feel about our status so far as arteriography is concerned: We are wanting in experience and it is only through the continued work and continued performance of this procedure, which we expect to continue to do, that we will be able to obtain adequate information so that ten years from now, at a meeting of this kind, we can sit down and say, "These are the facts about arteriography from correlation of the arteriogram with the pathological specimen in two thousand cases collected from your clinic and ours."

A NONOPAQUE ROENTGENOGRAPHIC AND WATER-REPELLENT EXAMINING TABLE MAT

M. SWICK

From the time of my original contribution with iopax and hippuran for excretory urography, it occurred to me that it would be advantageous if a durable, water-repellent mat could be developed to enhance the comfort of the patient on the usually hard x-ray and examining table, and yet not detract from the efficiency, definition, and clarity of the roentgenologic result. The debilitated and bony individual in particular finds the average table rather uncomfortable.

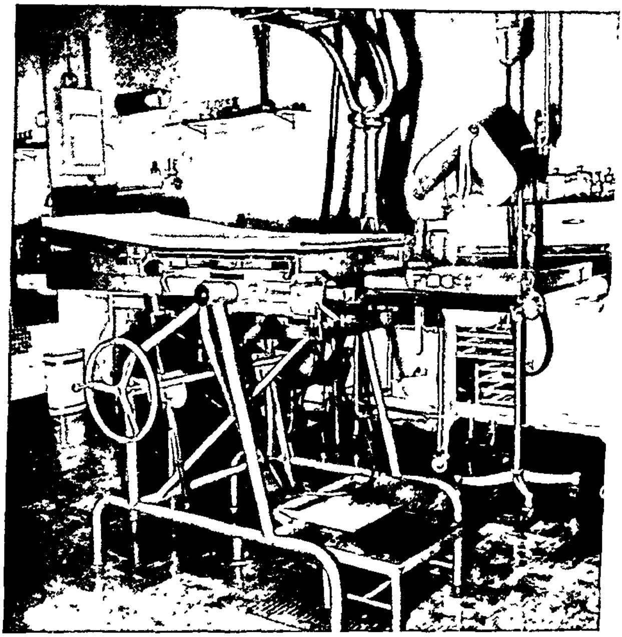

FIG. 1. Two piece mat in place on Young urologic table

I have found the answer to this problem in the following described mat (fig. 1). The latter is 1 to 2 inches in thickness and is snugly pillow-cased within a specially devised rubber cover arranged with a zipper at one end. This cover is removable, replacable, water-repellent, and can be dried instantly; greasy materials such as vaseline may be easily removed with dilute tincture of green soap and water, and if necessary, alcohol, without affecting its durability. Various dyes can be easily removed in this manner. Following the removal of greasy materials with the dilute tincture of green soap and alcohol, a slight roughness of the surface of the cover may ensue. This, however, may easily be overcome with the application of a small amount of finely powdered corn starch which restores the original

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This product may be secured from the Non-Opaque Pad Company, 640 North Avenue, New Rochelle, N. Y.

softness and smoothness. Such applications may be made repeatedly without in any way affecting the character of the mat. Since the mat is water-repellent, it

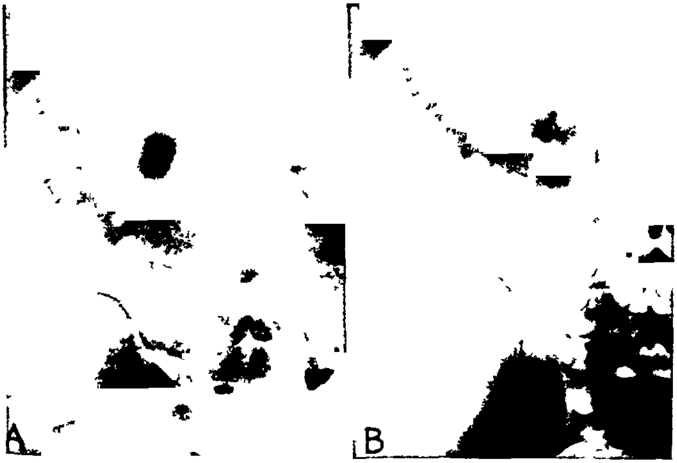

FIG 2 A, without mat Small calculus in lower pole of right kidney. *B*, same case, with mat

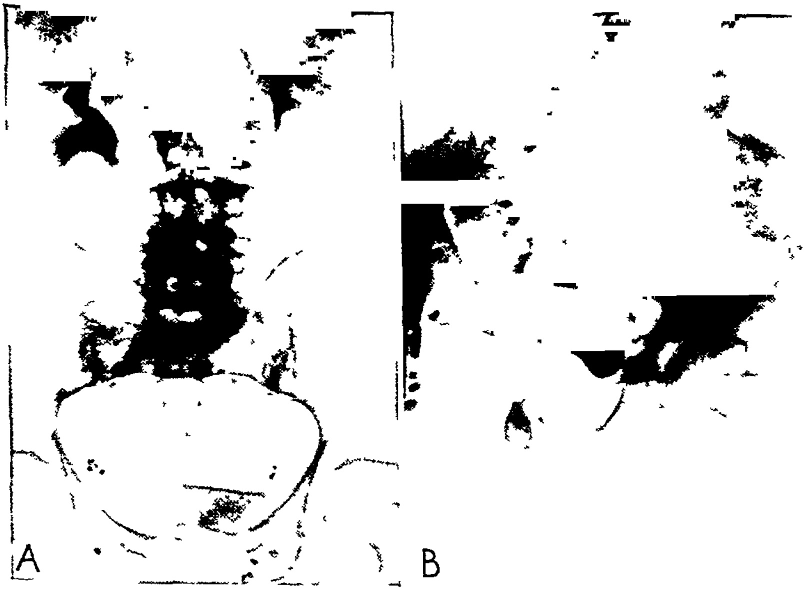

FIG 3 A, with mat Excretory urogram in case of urethral diverticulum Normal upper urinary tract, dilatation of pelvis and calyces on right side, slight elevation of base of bladder *B*, same case, without mat Urethrogram depicting diverticulum.

can be kept dry and clean from patient to patient. It is to be noted that the mat is insured in this manner against impregnation with and contamination from various opaque substances that are commonly in use for x-ray purposes.

The mat is manufactured either as a one full length piece for the average sized roentgenologic and examining table, or in two pieces (head-trunk, and leg-foot sections) for the typical urologic table with removable leg and foot piece.

The following reproductions of x-ray films illustrate the results obtained with the mat under various conditions. One can note the clarity, definition, and distortion-free roentgenographic results (figs. 2 and 3).

In conclusion, I believe that the mat represents a contribution to the much needed comfort to the patient during various types of roentgenographic examinations without in any way sacrificing the efficiency of the x-ray results.

19 E. 83rd St., New York, N. Y.

PROGRAM, ANNUAL MEETING, AMERICAN UROLOGICAL ASSOCIATION, THE PALMER HOUSE, CHICAGO, ILL.

MONDAY, MAY 21, 1951

8:00 A.M.-9:00 A.M.

Motion Pictures

Female Urinary Stress Incontinence (13 minutes)
Robert Lich Jr. and (by invitation) Joseph A. Maurer, Louisville, Kentucky

Repair of Vesicovaginal Fistula (12 minutes)
Roger W. Barnes and R. Theodore Bergman, Los Angeles, California

Ectopic Vagino-Ureteral Orifice (20 minutes)
Charles M. Stewart, Los Angeles, California

9:00 A.M.-12:00 N.

Interstitial Cell Tumor of the Testicle
Morton M. Mayers, Los Angeles, California

From the literature are derived 39 cases of interstitial cell tumor of the testicle, the author adding three. Their relationship to hyperplasia of the cells of Leydig, their characteristics particularly relating to endocrine changes, and a possible confusion with Sertoli cell tumor are discussed.

DISCUSSION

Lloyd G. Lewis, Washington, D. C.

Laboratory Controls in Carcinoma of the Prostate: Estrogenic and Androgenic Effects
Philip West and Donald Malcolm (by invitation) and Carl Rusche, Hollywood, California

Active carcinoma is associated with disturbances in balance between chymotrypsin and rennin inhibitors of serum. Sensitivity of these anti-enzymes to neoplastic activity is demonstrated by rapid changes following orchiectomy or steroid administration in prostatic carcinoma. Prompt determination of optimum dosage and hormone effectiveness may be made by this relatively simple procedure.

DISCUSSION

William W. Scott, Baltimore, Maryland

The Sequelae of Prostatic Surgery
M. Leopold Brodny and (by invitation) Samuel A. Robins, Boston, Massachusetts

A urethrographic study was made to determine the etiology of persistent and recurrent symptoms after prostatectomy. Every type of prostatectomy was investigated preoperatively, immediately postoperatively, and many months to years after surgery. The causative factors are classified and visualized by typical urethrograms. The prevention of these sequelae are discussed. Scientific Exhibit.

DISCUSSION

Samuel A. Vest, Charlottesville, Virginia

A New Hemostatic Agent
J. Sydney Ritter and (by invitation) Henry Bloomberg, New York, New York

This hemostatic material is composed primarily of compressed starch. Its action depends on mechanical pressure. No irritating or caustic reaction follows its employment. Material has been adapted in all prostatic operative procedures for the past eight months and no untoward reaction has been noted.

DISCUSSION

Samuel A. MacDonald, Montreal, Quebec

Presentation of Sixth Annual Award for Research on Male Reproductive Tract
By Reed M. Nesbit, Chairman Award Committee

Recipient for 1951:

John MacLeod, Ph.D., Associate Professor of Anatomy, Cornell University Medical College, New York, New York

Address by Dr. MacLeod:

Certain Concepts in Human Male Fertility

TUESDAY, May 22, 1951

8:00 A.M.–9:00 A.M.

Motion Pictures

Extirpation of the Penis (16 minutes)
Frederick A. Lloyd, Chicago, Illinois

Two Stage Operation for Hypospadias (20 minutes)
Harry M. Spence and Sydney S. Baird, Dallas, Texas

Tumors of the Testis (20 minutes)
James C. Sargent, Milwaukee, Wisconsin

9:00 A.M.–12:30 P.M.

Scientific Sessions

Histological Study of Vesical Urothelium Intervening Between Gross Neoplasms in Total Cystectomy
Meyer M. Melicow, New York, New York

Excision or any other means of eradication of a bladder neoplasm is often followed at varying intervals with development of one or more additional tumors. Total cystectomy offers a chance to determine whether such development is a "recurrence" or an independent process. If microscopic foci of precancerous and neoplastic tissue can be found intervening between obvious bladder tumors, then we are not dealing with "recurrences" but rather with the development of new tumors whose onset, on a microscopic basis, took place before surgical intervention.

DISCUSSION

Edwin F. Hirsch (by invitation), Chicago, Illinois

Carcinoma of the Bladder: Influence of Depth of Infiltration on the Five-Year Results Following Complete Extirpation of the Primary Growth
Hugh J. Jewett, Baltimore, Maryland

The results strongly suggest that tumors, regardless of histological pattern and degree of malignancy, which have infiltrated less than half way through the muscularis usually are confined to the bladder wall; and tumors which have infiltrated more deeply usually have spread beyond it.

DISCUSSION

Roger C. Graves, Boston, Massachusetts

Restudy of the First 1400 Tumors in the Bladder Tumor Registry
Archie L. Dean, New York, New York, F. K. Mostofi and (by invitation) R. V. Thomson, Washington, D. C.

In 1936 a statistical study of the first 1400 bladder tumors in the Registry was presented by the Registry Committee. The Registry Committee has now re-examined 1100 of these cases on which follow-up information to 1950 was available.

DISCUSSION

William A. Milner, Albany, New York

Vesico-Urethral Reflux in the Paraplegic: Cause and Correction (*First Prize Essay*)
John A. Hutch (by invitation), Richmond, Virginia

This essay concerns itself with an operation designed to correct vesico-ureteral reflux and with the theoretical conceptions upon which this operation was devised. (See Motion Picture Program for Tuesday afternoon.)

DISCUSSION

Herbert S. Talbot, Framingham, Massachusetts

Recess (20 minutes)

Bladder Electromyography: A New Approach to the Diagnosis of Urinary Bladder Dysfunction (Second Prize Essay)
William H. Boyce (by invitation), Charlottesville, Virginia

Muscular activity of the intact human bladder is preceded and accompanied by electropotential changes which can be translated into characteristic wave forms by a suitable electronic technique. Injury to either the bladder musculature or bladder innervation produces changes in these electropotentials which may be readily identified on the oscillographic record. Scientific Exhibit.

DISCUSSION

Charles B. Huggins, Chicago, Illinois

Subtotal Cystectomy for Atonic Bladder
Louis M. Orr, Orlando, Florida

Resection of the major portion of the urinary bladder for reduction of residual urine was first reported by the author in 1936. Since that time the operation has been successfully applied to atonic bladders of neurogenic as well as myogenic origin, both congenital and acquired.

DISCUSSION

George O. Baumrucker, Cicero, Illinois

A Method for Establishing Portal Drainage of Adrenal Venous Blood in Dogs with Metabolic Studies Included (Third Prize Essay)
John T. Grayhack and A. Page Harris (by invitation), Baltimore, Maryland

Previous experimental work indicates that liver inactivates androgens. Life-sustaining adrenal steroids are not completely inactivated. The venous blood flow of a dog's remaining adrenal becomes primarily portal when renal-splenic venous anastomosis is performed in a Levy-Blalock type preparation. Dogs can survive this procedure. Electrolyte and carbohydrate metabolism remain relatively normal.

DISCUSSION

Seymour F. Wilhelm, New York, New York

A Study of Bilateral Total Adrenalectomy in Malignant Hypertension and Chronic Nephritis: Preliminary Report
George W. Thorn (by invitation), J. Hartwell Harrison and (by invitation) Modestino G. Criscitiello, Boston, Massachusetts

Bilateral complete adrenalectomy has been performed upon ten patients having severe malignant hypertension in varying stages of cardiovascular renal disease. The medical and surgical management as well as the physiological changes induced in these patients will be described. Adequate substitution therapy with cortisone, adrenal extract, desoxycorticosterone and electrolyte solutions has made this radical approach a feasible operative procedure in patients with serious vascular disease. Other implications will be discussed.

DISCUSSION

George F. Cahill, New York, New York

TUESDAY, MAY 22, 1951

2:00 P.M.–5:00 P.M.

Motion Pictures

Diverticulum of the Female Urethra (8 minutes)
Virgil S. Counseller, Rochester, Minnesota

Radical Operation for Tumor of the Urethra (15 minutes)
J. A. Campbell Colston, Baltimore, Maryland

A New Concept of Management in Exstrophy of the Bladder (25 minutes)
William H. Boyce (by invitation) and Samuel A. Vest, Charlottesville, Virginia

Vesico-Ureteroplastic Operation for Reflux (12 minutes)
John A. Hutch (by invitation) and R. Carl Bunts, Richmond, Virginia

The Dorsolumbar Flap Incision in Urologic Surgery (20 minutes)
George R. Nagamatsu, New York, New York

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The Dorsolumbar Flap Incision in Urologic Surgery (20 minutes)
George R. Nagamatsu, New York, New York

Recess (15 minutes)

Hemisection of Horseshoe Kidney (15 minutes)
Oswald S. Lowsley, New York, New York

Bilateral Caliceal Diverticulectomy (15 minutes)
N. R. Varano and T. G. Hurdle (by invitation) and Albert A. Creecy, Newport News, Virginia

Diagnosis and Management of Bilateral Multiple Pheochromocytomas (12 minutes)
Knowlton E. Barber, Chicago, Illinois

Operative Treatment of Polycystic Kidney (12 minutes)
Maj. Evan L. Lewis (by invitation) and Col. James C. Kimbrough, Washington, D. C.
Plastic Tubes for Ureteropelvioplasty (18 minutes)
William L. McLaughlin (by invitation) and John P. Bowler, Hanover, New Hampshire

WEDNESDAY, MAY 23, 1951

8:00 A.M.-9:00 A.M.

Motion Pictures

The Nagamatsu Technique as Applied to Retroperitoneal Dissection (15 minutes)
Brice S. Vallett, Wilmington, Delaware

One-Stage Suprapubic Prostatectomy with Primary Bladder Closure (15 minutes)
George H. Ewell and Harold W. Bruskewitz, Madison, Wisconsin

Transurethral Prostatic Resection (12 minutes)
Roger W. Barnes and R. Theodore Bergman, Los Angeles, California

9:00 A.M.-12:30 P.M.

Scientific Sessions

Transurethral Endovesical Ureterolithotomy with the Resectoscope
Edwin Davis, Leroy W. Lee and (by invitation) Edwin Davis, Jr., Omaha, Nebraska

In evaluating the methods of treatment for calculi impacted in the intramural portion of the ureter, transurethral endovesical ureterolithotomy with the resectoscope appears to have many advantages over the methods in common usage because of its simplicity, safety, short period of hospitalization, and satisfactory end result.

DISCUSSION

William M. Coppridge, Durham. North Carolina

Nephro-Ureterectomy: A New Technique
Harold P. McDonald, Atlanta, Georgia

Nephro-ureterectomy, an operation usually requiring two incisions, is simplified by transurethral electroresection of ureter from the bladder before removal of the kidney. Nephrectomy is done immediately and the lower ureter removed along with the kidney through the ordinary kidney incision. (See Motion Picture Program for Thursday morning.)

DISCUSSION

Charles C. Higgins, Cleveland, Ohio

Experimental Studies on Uretero-Enterostomy
Lorande M. Woodruff and John F. Cooper (by invitation) and Wyland F. Leadbetter, Boston, Massachusetts

Uretero-enterostomy has been performed on dogs utilizing several common operative techniques. Studies have been made to compare healing at the site of anastomosis by sacrificing animals at intervals. Ureteral function has been evaluated by hydrodynamic and electromyometric tests. An effort has been made to determine whether any technique gives superior results.

Evaluation of Common Methods of Uretero-Intestinal Anastomosis
Henry M. Weyrauch and (by invitation) Bradford W. Young, San Francisco, Calif.

Critical analysis of the submucosal channel, the intraluminal segment and the mucosa-to-mucosa principle. Studies are reported concerning leakage, reflux, upper urinary obstruction and ascending infection following various methods of transplantation in 40 dogs. Deductions are drawn as to ideal operative technique.

DISCUSSION

Justin J. Cordonnier, St. Louis, Missouri

Carl A. Wattenberg, St. Louis, Missouri

Recess (20 minutes)

Plastic Surgery of the Ureter in Children

John K. Ormond and (by invitation) Robert W. Osborne, Detroit, Michigan

The indications for plastic operations on the ureter in children may occur at either end of the ureter. This is the report of a short series of cases in which plastic operations were done. The results of operation at the upper end of the ureter were good but at the lower end not so good.

DISCUSSION

Meredith F. Campbell, New York, New York

The Use of Segments of Small Intestine as Ureters

Don W. McLean and O. G. Fais (by invitation), Detroit, Michigan

20 cm. segments of terminal ileum were used to replace one or both ureters in twelve dogs. Chemical, bacteriological and histological studies were made before and for periods up to one year following surgery. Infection and some degree of obstruction of the uretero-intestinal anastomosis were present in all cases. Absorption of urinary constituents from small intestine did not appear significant factor.

DISCUSSION

Reed M. Nesbit, Ann Arbor, Michigan

Problems Associated with Ureteral Tumors

Morris R. Keen, Huntington, New York

A series of five ureteral tumors with associated diagnostic and therapeutic problems is presented. A high incidence (1:1200 cases) is noted. The pathogenesis of these tumors is reviewed and evaluated by the use of mitochondrial and Golgi stains in three cases.

DISCUSSION

Vincent J. O'Conor, Chicago, Illinois

Hematuria in Sickle Cell Anemia

Francis G. Harrison and (by invitation) Francis G. Harrison, Jr., Philadelphia, Pennsylvania

Discussion of the pathology and physiology of sickle cell anemia with survey of the frequency of the disease and consideration of treatment. Case reports of patients having unilateral renal involvement with subsequent improvement with medical treatment or nephrectomy. An attempt is made to explain the unilateral occurrence.

DISCUSSION

Raymond F. Mayer, Memphis, Tennessee

WEDNESDAY, MAY 23, 1951

2:00 P.M.-5:00 P.M.

Presidential Address

For the Good of the Order

Thomas D. Moore, Memphis, Tennessee

The Ramon Guiteras Lecture

The Kidney and Hypertension

George E. Wakerlin, Professor of Physiology, University of Illinois College of Medicine, Chicago, Illinois

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Recess (20 minutes)

Business Meeting

Recess (15 minutes)

Hemisection of Horseshoe Kidney (15 minutes)
Oswald S. Lowsley, New York, New York

Bilateral Caliceal Diverticulectomy (15 minutes)
N. R. Varano and T. G. Hurdle (by invitation) and Albert A. Creecy, Newport News, Virginia

Diagnosis and Management of Bilateral Multiple Pheochromocytomas (12 minutes)
Knowlton E. Barber, Chicago, Illinois

Operative Treatment of Polycystic Kidney (12 minutes)
Maj. Evan L. Lewis (by invitation) and Col. James C. Kimbrough, Washington, D. C.

Plastic Tubes for Ureteropelvioplasty (18 minutes)
William L. McLaughlin (by invitation) and John P. Bowler, Hanover, New Hampshire

WEDNESDAY, MAY 23, 1951

8:00 A.M.–9:00 A.M.

Motion Pictures

The Nagamatsu Technique as Applied to Retroperitoneal Dissection (15 minutes)
Brice S. Vallett, Wilmington, Delaware

One-Stage Suprapubic Prostatectomy with Primary Bladder Closure (15 minutes)
George H. Ewell and Harold W. Bruskewitz, Madison, Wisconsin

Transurethral Prostatic Resection (12 minutes)
Roger W. Barnes and R. Theodore Bergman, Los Angeles, California

9:00 A.M.–12:30 P.M.

Scientific Sessions

Transurethral Endovesical Ureterolithotomy with the Resectoscope
Edwin Davis, Leroy W. Lee and (by invitation) Edwin Davis, Jr., Omaha, Nebraska

In evaluating the methods of treatment for calculi impacted in the intramural portion of the ureter, transurethral endovesical ureterolithotomy with the resectoscope appears to have many advantages over the methods in common usage because of its simplicity, safety, short period of hospitalization, and satisfactory end result.

DISCUSSION

William M. Coppridge, Durham. North Carolina

Nephro-Ureterectomy: A New Technique
Harold P. McDonald, Atlanta, Georgia

Nephro-ureterectomy, an operation usually requiring two incisions, is simplified by transurethral electroresection of ureter from the bladder before removal of the kidney. Nephrectomy is done immediately and the lower ureter removed along with the kidney through the ordinary kidney incision. (See Motion Picture Program for Thursday morning.)

DISCUSSION

Charles C. Higgins, Cleveland, Ohio

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Lorande M. Woodruff and John F. Cooper (by invitation) and Wyland F. Leadbetter, Boston, Massachusetts

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Recess (20 minutes)

Business Meeting

President's Cocktail Party, 6:45 P.M.

Banquet, 8:00 P.M.

THURSDAY, MAY 24, 1951

8:00 A.M.-9:00 A.M.

Motion Pictures

A New Technique for Nephro-Ureterectomy (15 minutes)
Harold P. McDonald, Atlanta, Georgia

Transurethral Prostatectomy (15 minutes)
Walter A. Keitzer, Akron, Ohio

Renal Arteriography by the Percutaneous Route (18 minutes)
Benjamin S. Abeshouse, Baltimore, Maryland

9:00 A.M.-12:30 P.M.

Scientific Sessions

The Problem of the Non-Opaque Urinary Stone
S. Richard Muellner and (by invitation) Bernard J. Sears, Boston, Massachusetts

Non-opaque stones may present unusual diagnostic difficulties. The search for the cause of acute pain, hematuria, or chills and fever can be misdirected by the inability to identify the stone. What the stumbling blocks are and how to avoid them are discussed.

The Role of Gout in the Formation of Urinary Calculi
W. E. Kittredge and (by invitation) Ralph Downs, New Orleans, Louisiana

The role of gout in the etiology of stone, poorly emphasized in the past, has been shown by our experience to be of great importance. When gout is present, the handling of the urologic problem is simplified by controlling the gout. Striking instances of this are described and the literature reviewed.

DISCUSSION

Rubin H. Flocks, Iowa City, Iowa

William P. Herbst, Washington, D. C.

The Clinical Evaluation of Aluminum Gels and Diets Low in Phosphorous for the Prevention of Renal Phosphatic Calculi
James L. Green (by invitation) and Victor F. Marshall, New York, New York

The aluminum gel-dietary regimen of Shorr for the prevention of urinary phosphatic calculi has been evaluated by comparing courses of 37 stone-forming patients before and during this regimen. A drastic reduction in stone formation occurred, which appears due to the prophylaxis. Chemical controls were used throughout study.

DISCUSSION

Richard W. Satterthwaite, Ancon, Canal Zone

Streptomycin and PAS Treatment of Genito-Urinary Tuberculosis
John K. Lattimer and Archie L. Dean, New York, New York

The Research Group for Genito-Urinary Tuberculosis of the Veterans Administration reports a new series of cases treated with streptomycin 1 gm. and PAS 12 gm. daily. The results are compared with those in a large group treated with streptomycin alone. Both renal and prostatic lesions were improved.

DISCUSSION

Frederick A. Lloyd, Chicago, Illinois

Recess (20 minutes)

Urologic Manifestations Associated with Aneurysm of the Abdominal Aorta
Lloyd R. Reynolds, Thomas L. Schulte and Howard J. Hammer, San Francisco, Calif.

Several patients having pain simulating ureteral colic were found to have abdominal aneurysms. Following spontaneous rupture of the aneurysms, postmortem findings are presented in 32 cases reviewed. Evidence was obtained to indicate that the possibility of abdominal aneurysm must be considered as an etiologic factor of ureteral colic in certain patients.

DISCUSSION

Charles A. W. Uhle, Philadelphia, Pennsylvania

Urinary Disease Resulting from Non-Malignant Conditions of the Intestine
Harrison Harlin (by invitation) and Frank C. Hamm, Brooklyn, New York

A presentation of clinico-pathological changes, with associated symptomatology, of the kidney, ureter, urinary bladder and retroperitoneum resulting from primary nonspecific inflammatory disorders of the gastro-intestinal tract. Case abstracts and illustrations accompany this discussion.

DISCUSSION

John E. Emmett, Rochester, Minn.

Aberrant Renal Arteries Which in Themselves Produce Pain
Nelse F. Ockerblad, Kansas City, Missouri

In this small series of cases it has been proven that the aberrant renal artery was itself the cause of pain without appreciable hydronephrosis. Each case was carefully studied, operated upon and followed completely.

DISCUSSION

Thomas E. Gibson, San Francisco, California

Indications for Nephropexy
Cyrus E. Burford, Joseph E. Glenn and E. Humber Burford, St. Louis, Missouri

A brief resume of the kidney of movable kidney, a detailed report of over 300 nephropexies, and criteria for selection of cases for surgery, as determined in over thirty-five years of experience with nephropexy.

DISCUSSION

Clyde L. Deming, New Haven, Connecticut

THURSDAY, MAY 24, 1951

2:00 P.M.-5:00 P.M.

Excretory Urography in the Diagnosis of Ureteropelvic Obstruction
William L. McLaughlin (by invitation) and John P. Bowler, Hanover, New Hampshire

The fact that urine containing contrast medium gravitates to the most dependent portion of the kidney can be used to improve the excretory urographic delineation of the renal pelvis. Roentgenograms at delayed intervals in the anteroposterior, posteroanterior and erect positions help to establish the diagnosis of uteropelvic obstruction in selected patients without retrograde urograms.

DISCUSSION

W. Joseph McMartin, Omaha, Nebraska

The Experimental and Clinical Investigation of Various Media Used in Translumbar Aortography
William F. Melick and (by invitation) Tom Boler and John W. Byrne, St. Louis, Missouri

All of the deaths from translumbar aortography have been attributed to the inadvertent injection of a necrosing medium into the superior mesenteric artery. Experimental work on dogs shows that this accident need no longer be feared with a new medium, which gives comparable clinical results to 80 per cent sodium iodide. Scientific Exhibit.

DISCUSSION

Parke G. Smith, Cincinnati, Ohio

American Board of Urology, Inc.: Its Activities During the Last Fifteen Years
Gilbert J. Thomas, President of the American Board of Urology, Inc., Beverly Hills, California

A history in abstract of the Board's activities, with a statistical report of the work accomplished, and a resume of the reasons for changes in the qualification requirements for candidates.

The Dorsolumbar Flap Incision in Urologic Surgery
George R. Nagamatsu and (by invitation) Philip Lerman and Michael Berman, New York, New York

Accumulated experience with this technique has expanded its applicability to include more radical forms of renal surgery, bilateral simultaneous adrenal exposure, retroperitoneal gland dissection for testicular tumor, bilateral renal surgery and thoraco lumbar sympathectomy Added safety and greater ease of execution are outstanding advantages (See Motion Picture Program for Tuesday afternoon)

Radical Nephrectomy for Neoplasm

Frederic E B Foley and (by invitation) William P Mulvaney, Edward J Richardson and Irving Victor, St Paul, Minnesota

A radical form of nephrectomy for renal neoplasm is presented The operation, accurately described and illustrated, is based on a definite anatomic plan in keeping with long recognized principles of surgery for malignant neoplasm not previously applied to nephrectomy

DISCUSSION

Theodore H Sweetser Minneapolis, Minnesota

Richard Chute, Boston, Massachusetts

Surgery of the Horseshoe Kidney

Oswald S Lowsley, New York, New York

The presence of horseshoe kidney is much less rare than formerly thought Such kidneys are particularly prone to disease and are usually curable by operation Pain is often elicited by the pressure of the isthmus upon the great vessels and this can also be eliminated by operative intervention Scientific Exhibit (See Motion Picture Program for Tuesday afternoon)

DISCUSSION

Robert B. McIver, Jacksonville, Florida

Renal Bisection A New Method

George W Slaughter, New York, New York

This is based on approximately 80 cases of extensive nephrostomies for large dendritic calculi Included in this series are eight solitary kidneys

DISCUSSION

Samuel K. Bacon, Hollywood, California

Induction of Incoming President

Adjournment

SCIENTIFIC EXHIBIT*

Dr Samuel A Vest, *Chairman*

1 *Genital Self Mutilations by Mental Patients*
Leon M Berlin, Chicago, Illinois
2 *Bladder Electromyography A New Approach to the Normal and Pathologic Physiology of the Urinary Bladder*
William H Boyce (by invitation) and Samuel A Vest, Charlottesville, Virginia
3 *The Sequelae of Prostatic Surgery*
M Leopold Brodny and (by invitation) and Samuel A Robins, Boston, Massachusetts
4 *Photographic History of the American Urological Association*
Wirt B Dakin, Los Angeles, California
5 *Hypotonic Dysfunctions of the Bladder with Particular Reference to Urecholine*
Edwin Davis and Leroy W Lee, Omaha, Nebraska
6 *Traumatic Avulsion of the Scrotum and Skin of the Penis*
George H Ewell and Harold W Bruskewitz, Madison, Wisconsin
7 *Distribution of Urologists in the United States and Its Possessions*
Franklin Farman and (by invitation) Leslie Kamens and Ruth Greider McCandless, Whittier, California

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* The Scientific Exhibit has been erected under the supervision of the Director of Exhibits, Mr William P Didusch

8. *Carcinoma of the Prostate*
   Rubin H Flocks, Iowa City, Iowa
9. *The Human Testis: The Effect of Testosterone upon Its Function*
   Norris J. Heckel and (by invitation) John Baylor and James T. McDonald, Chicago, Illinois
10. *Radiocobalt in the Treatment of Bladder Tumors*
   Frank Hinman, Jr., John W. Schulte and Bertram V. A. Low-Beer (by invitation), San Francisco, California
11. *Clinical Significance of the Para-Urethral Ducts and Glands*
   John W. Huffman (by invitation), Chicago, Illinois
12. *A Technique for Nephropexy after Pre-Surgical Evaluation*
   R Frank Jones (by invitation), Washington, D. C.
13. *Artificial Kidney*
   Walter A. Keitzer, Akron, Ohio
14. *Surgery of the Horseshoe Kidney*
   Oswald S. Lowsley, New York, New York
15. *Experimental Studies on Various Media Used for Translumbar Aortography and a New Medium 70 per cent Urokon*
   William F Melick and (by invitation) John W. Byrne and Tom Boler, St. Louis, Missouri
16. *A New Type Needle Sharpener*
   William A Milner, Albany, New York
17. *Management of Ureteral Injury in Open Pelvic Surgery*
   Ralph B Mullenix and Robert J Prentiss, San Diego, California
18. *New Type of Artificial Kidney Design (Rosenak-Saltsman)*
   Gordon D. Oppenheimer and (by invitation) Stephan S. Rosenak, New York, New York
19. *Bedside Urological X-Ray Examination of the Injured Patient*
   Lazarus A Orkin, New York, New York
20. *The Reproduction of X-Rays on 35 MM Film*
   Norborne B Powell, Houston, Texas
21. *Translumbar Arteriography in the Diseases of Renal Masses*
   Parke G Smith and (by invitation) Thomas W Rush and Arthur T. Evans, Cincinnati, Ohio
22. *Abacterial Pyuria*
   Harry M Spence and (by invitation) Kenneth Mooney, Dallas, Texas
23. *Perirenal Insufflation by Cannula Proposal of a Safer and More Accurate Method*
   Harry R Trattner and (by invitation) Elihu Klein, Harold E. MacDonald and J. Montgomery Beck, Cleveland, Ohio

TECHNICAL EXHIBIT

Mr William P. Didusch, *Director*

NAME AND ADDRESS OF EXHIBITOR	BOOTH
Abbott Laboratories, North Chicago, Ill.	11
Allis Chalmers Manufacturing Co , Milwaukee, Wis.	32
American Cystoscope Makers, Inc , New York, N. Y.	14, 15, 16, 17, 18, 19, 20, 21, 22, 23
Americana Corporation, Chicago. Ill.	43
C. R Bard Inc , Summit, N J	6, 7, 8
Bilhuber Knoll Corporation, Orange, N J	38
Birtcher Corporation, Los Angeles, Cal	4
Ciba Pharmaceutical Products, Inc , Summit, N. J.	40
Coca Cola Co , Atlanta, Ga.	5
Eaton Laboratories, Inc , Norwich, N Y.	34
Encyclopaedia Britannica, Chicago, Ill.	42
Ethicon Suture Laboratories, New Brunswick, N. J.	28
Grune and Stratton, Inc , New York, N. Y.	29
Hoffmann-LaRoche, Inc , Nutley, N J.	49
Kalak Water Co of New York, New York, N. Y.	30
Lederle Laboratories, New York, N. Y.	27
Liebel Flarsheim Co , Cincinnati, O	37

Mallinckrodt Chemical Works, St. Louis, Mo.	47, 48
Merck and Co., Inc , Rahway, N. J.	39
V. Mueller and Co., Chicago, Ill.	9, 10
Nepera Chemical Co., Inc., Yonkers, N. Y.	3
Ohio Chemical and Surgical Equipment Co., Madison, Wis.	45
Charles Pfizer & Co., Inc., Brooklyn 6, N. Y.	33
Parke, Davis and Co., Detroit, Mich	36
Philip Morris & Co. Ltd., Inc , New York, N. Y.	41
Radium Chemical Co., New York, N. Y	12
Radium Emanation Corporation, New York, N. Y.	1
Schering Corporation, Bloomfield, N. J.	2
St. Anthony Machine Products Co , Minneapolis, Minn.	13
E R. Squibb and Sons, New York, N. Y.	46
Vanpelt and Brown, Inc , Richmond, Va.	44
Williams and Wilkins Co., Baltimore, Md.	24
Winthrop Stearns, Inc , New York, N. Y..	25, 26

THE JOURNAL OF UROLOGY
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SOME HOMEOSTATIC FUNCTIONS OF THE KIDNEY

THOMAS FINDLEY

From the Departments of Medicine, Tulane University of Louisiana, School of Medicine and the Ochsner Clinic, New Orleans, La.

It was a pleasant privilege to accept your invitation to give this lecture. I am here with some misgivings, however, because I am not sure that I can say anything which will seem important to you and because the duty of memorializing someone I never knew seems formidable and even a bit eerie. I have made inquiries, though, which have given me some notion as to what sort of man Dr. Edgar Garrison Ballenger was, and somehow I do not think he would mind if I begin by saying that urologists possess one common quality which I cannot understand.

All the urologists I know are grand fellows whose immense technical skill I never cease to envy, but they simply are not interested in the kidney. They are, to be sure, passionately devoted to abscesses, tumors or deformities of the kidney, but I think it not unfair to suggest that they give this wonderful organ little thought unless it is afflicted by some peculiarly loathsome disease. The silent but vital role it plays in maintaining that state of equilibrium known as "good health" seems not to excite them but it excites me, so I propose to give you three examples which illustrate how apparently trivial failure of the kidney to make the proper response may disastrously affect the whole body economy.

The first portion of my talk will be on the responses of the kidney to a failing circulation, since this is the key to the problem of edema. Secondly, I will comment upon the role of the kidney in the production and maintenance of high blood pressure, and lastly, I will have something to say about the manner in which disturbances of acid-base balance may deform the skeleton and precipitate urinary stone. Many other examples might be given but these are enough to illustrate the fact that disease is often what the word says it is—*dis-ease* or *disequilibrium* or failure of homeostasis.

If one holds a test tube of blood and a test tube of urine side by side, he cannot fail to suspect that a remarkable machine has been at work, and the wonder is increased if he compares the concentrations of the various chemical substances in the two materials. This should not lead him into two errors of judgment: a) that the function of the kidney is to make urine, and b) that the kidney is an efficient organ. As to the first, it need only be said that the true function of the kidney is to insure the chemical constancy of the blood, urine having no function of which I am aware. As to the second, one has only to remember that the kidney comes in two parts, so to speak; the glomerular membrane which enables the heart to pump an enormous amount of water and solutes out of the blood stream, and the tubules whose instant duty it is to return virtually all this vital fluid to the vessels from whence it came. No engineer in his right mind would have designed such an extravagant organ as this but there are evolutionary

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The Edgar Ballenger Memorial lecture.
Read at annual meeting, Southeastern Section, American Urological Association, Gulfport, Miss., February 3, 1950.

reasons for its peculiar structure,[1] and in a very real sense our lives depend upon maintenance of this balance between glomeruli and tubules. Let us see how "glomerulotubular imbalance" disrupts homeostasis.

HOW THE KIDNEY SUPPORTS A FAILING CIRCULATION

The mammalian circulation cannot be compared with a simple pump set into a closed hydraulic system; if it were similar, cardiac failure would result only in stagnation of the stream without venous distention or edema. Actually, the heart has two pumps: the right and the left, a circumstance which enormously complicates the situation. In addition, that part of the circulation which lies between the right and the left sides is partially enclosed in a bellows arrangement known as the lung, and this adds further difficulties because it subjects this part of the circulation to changes in external pressure. Even so, it is most significant that after a patient is dead of heart-failure and the pump has entirely stopped, the pressure within the veins remains high,[2] a clear indication that the volume of fluid within them has been increased, and had the corpse been appropriately studied before the heart had stopped, the source of this extra fluid would have become apparent, for the rate of blood flow through the kidneys was sharply curtailed during life[3] and the ability to excrete salt and water considerably diminished.[4]

This reduction in renal blood flow, glomerular filtration rate and clearance of salt and water occurs whenever the circulation fails for whatever reason, and the degree to which these renal functions are impaired exceeds by a considerable amount the degree to which the circulation as a whole is impaired; that is to say, a reduction in cardiac output is accompanied by an even sharper decline in renal blood flow.[5] This is a curious phenomenon and there is no agreement among those interested as to its cause; since the renal anemia occurs even after the kidneys have been denervated, it is evidently not of reflex origin,[6] and there is therefore a tendency to suppose that the endocrine glands are somehow activated by circulatory failure in such a manner as to cause the posterior pituitary or the adrenal cortex or both to secrete larger amounts of antidiuretic substances.[5]

Whatever the explanation may be for the fact that circulatory failure is followed by diversion of blood from the kidney elsewhere, the end result is retention of salt and water. Dock[7] has offered an ingenious teleological explanation for this phenomenon, pointing out that for countless generations mammals have been subjected to insults that reduce circulatory efficiency (hemorrhage, shock, dehydration, severe exertion) and that it would be surprising if a mechanism had not been evolved which automatically improves the circulation by expanding a shrunken blood volume. It seems to matter little whether circulatory efficiency is impaired by an inadequate amount of blood or by failure of the heart to meet bodily requirements; the end result is renal retention of salt water and, if the precipitating cause is irreversible, as in myocardial disease or chronic hypoproteinemia, the compensatory process continues blindly to a state of gross edema. The following examples may be cited: 1) since the cardiac output is sharply reduced in the erect position, the tired housewife notes that her ankles are swollen at the end of a long hot day; 2) the patient with myocardial infarction or prolonged paroxysmal tachycardia has rales in his lungs and a large sore liver; 3) congestive failure develops in a woman with thyrotoxicosis, not because of intrinsic cardiac disease but because the myocardium is simply unable to keep up with the demand of the tissues for oxygen; 4) five days after a gastric resection, an elderly man has what his doctor thinks is heart failure, because he has received excessive amounts of saline infusions at a time when his kidneys are retaining sodium in an effort to counteract the blood lost at operation; 5) dropsy develops in a patient with hypoproteinemia and a shrunken blood volume because of hepatic disease or nephrosis and 6) a woman with a sore tongue and a red cell count of less than 1,000,000 per cubic millimeter exhibits edema of the legs. Many other illustrations might be offered but these suffice to support the thesis that the kidney retains sodium and water whenever the circulation becomes unable to meet the needs of the body as a whole. Indeed, it seems possible to adopt a clinical rule that a normal output of urinary sodium excludes the possibility of circulatory failure. Unfortunately for the practitioner, however, the excretion of sodium does not always parallel that of chloride so that he cannot rely upon the simpler technical methods of determining urinary chloride.

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[1] Smith, H. W.: Lectures on the kidney. University of Kansas, Extension Division, Lawrence, Kansas, 1943.

[2] Starr, I.: Our changing viewpoint about congestive failure. Ann. Int. Med., 30: 1–23, 1949.

[3] Warren, J. V. and Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. Arch. Int. Med., 73: 138–147, 1944.

[4] Futcher, P. H. and Schroeder, H. A.: Studies on congestive heart failure; impaired renal excretion of sodium chloride. Am. J. M. Sc., 204: 52–62, 1942.

[5] Merrill, A. J.: Mechanisms of salt and water retention in heart failure. Am. J. Med., 6: 357–367, 1949.

[6] Mokotoff, R. and Ross, G.: Effect of spinal anesthesia on renal ischemia in congestive heart failure. J. Clin. Investigation, 27: 335–339 (pt. 1), 1948.

[7] Dock, W.: Physiological problems in treatment of heart disease. J. Mt. Sinai Hosp., 13: 310–317, 1947.

THE KIDNEY AS AN ENDOCRINE GLAND

At the moment it is fashionable to regard hypertension as an inherently evil condition. An enormous number of people with high blood pressure die prematurely, of course, and strenuous efforts are being made from various directions to devise methods of reducing blood pressure with the hope of diminishing this appalling mortality. The objective is praiseworthy but one is entitled to wonder if the life expectancy of an individual with hypertensive cardiovascular disease might not be even shorter if hypertension had not developed. This is equivalent to a suggestion that an elevation in blood pressure might initially be a compensatory and beneficial reaction to a disturbance of unknown nature. Analogies may readily be found among the small percentage of patients in whom a specific etiology for hypertension can be found. For example, hypertension develops in a child with coarctation of the aorta in an obvious effort to force the blood through the constricted segment, and no one would argue that treatment designed to lower the blood pressure by any means other than excision of the deformed aortic segment could be helpful. Again, hypertension develops in a person with a pheochromocytoma, chiefly because epinephrine increases the flow of blood into the heart; in such an instance, any method designed merely to lower the blood pressure can only be harmful. It is possible that ordinary essential hypertension also represents a compensatory reaction but the inciting disturbance is not yet known. So long as the causative mechanism operates, hypertension will not only persist but will intensify until ultimately the entire organism is destroyed. If a motorist is mired deeply enough in mud, a towcar may, with the best of intentions, jerk the bumper entirely off without affecting the fundamental problem in the least.

Some insight into the problem of hypertension may possibly be gained by noting the events which follow removal of the normal kidney. So far as I know the kidney is one of the few paired organs which enlarge after excision of their mates, and this is no simple "work hypertrophy" because it does not occur in any animal whose anterior pituitary or adrenal cortex has first been removed.[8] How then does such a simple procedure as unilateral nephrectomy activate the anterior pituitary—adrenocortical complex to secrete increased amounts of what may be termed "renotrophic hormone" and why does the remaining kidney not continue to grow indefinitely?

No didactic answers can be given but one may suppose that the remaining kidney, finding itself unable to do the work of two, secretes something into the blood stream which stimulates activity in an "anterior pituitary → adrenal cortex → renal tubules" direction until such time as the total mass of renal tissue reaches a size adequate for the body's metabolic needs. Heinbecker[8] believes that renin is the substance responsible for this remarkable chain of events, for it is formed in excessive amounts whenever the integrity of the renal tubules is threatened; he presents evidence, which has been reviewed elsewhere,[9] to show that renin so depresses the activity of the anterior lobe basophiles as to allow the eosinophiles to act in an unrestrained manner upon the adrenal cortex and its several target organs. We[8a] have, on the other hand, recently been privileged to study material, kindly supplied by Dr. Arthur Grollman, of some bilaterally nephrectomized dogs which he keeps alive by special technique; severe hypertension develops in these dogs in the complete absence of renal tissue, and their anterior pituitary glands reveal pronounced proliferation of the eosinophiles with diminution of the basophiles and chromophobes. It, therefore, seems to us that renal tubules may normally secrete something which depresses the functional activity of the eosinophile-adrenocortical complex, and that renal hypertension is a deficiency disease.

This is not the place to debate the virtues or defects of these intriguing theories; but it should be stated here that the kidney is, at least under stress, a part of the endocrine system, and that renin may properly be thought of as a renal hormone which protects homeostasis in at least two important ways:

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[8] Heinbecker, P.: Pathogenesis of diastolic hypertension. Surgery, 23: 618–638, 1948.

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1) Renin, or some other substance in renal tissue, diminishes the oxygen requirements of the kidney itself.[10] Renal ischemia increases renin formation and this permits the kidney to withstand long periods of complete anoxia in sharp contrast to the short viability of other tissues.

2) By its constricting action on extrarenal blood vessels renin raises blood pressure and by its capacity to increase cardiac output, tends to maintain renal blood flow.[8] It also preferentially constricts the efferent glomerular arterioles[11] and this tends to support the rate of glomerular filtration even in the face of a diminishing circulation.

I have dwelt at some length upon this post-nephrectomy syndrome simply for purposes of illustration. Clinically, the integrity of renal tissue is much more commonly threatened by such conditions as anoxia, infection or vascular disease; intermittent overactivity in the sympathetic nervous system and the adrenal medulla will cause periodic renal ischemia; and some adrenocortical steroids produce profound renal damage.[12] No implication is made here that hypertension is always of renal origin. The converse is probably true but these ideas have an important bearing on the practical problem of hypertension associated with unilateral kidney disease. I hope enough has been said to indicate that pyelonephritis or any other lesion leading to increased formation of renin merely sets a complicated chain of events into motion, and that hypertension which may obviously be of renal origin soon acquires an endocrine aspect which tends to perpetuate a vicious cycle. If nephrectomy is really to reverse the hypertensive process, I suspect it must be done in a matter of weeks after the initial rise in blood pressure.

HOW RENAL LESIONS AFFECT THE SKELETON

Any substantial increase in the hydrogen-ion concentration of body fluids is a serious threat which the kidney meets by a variety of exquisite adjustments. One of the more obvious counter measures is the excretion of acid radicals, acid phosphate being a particularly useful one because it enables one atom of base to carry two atoms of hydrogen with it out of the body (NaH_2PO_4), whereas in the alkaline formula, Na_2HPO_4, the reverse is true. Secondly, the kidney manufactures increased amounts of ammonia, a substance which readily combines with acid radicals and allows the body to retain equivalent amounts of base. If these two measures prove incapable of dealing with all the acids offered to the kidney, the body must lose basic ions, one of the most important of which is calcium. Finally, if the need is great enough, more base is withdrawn from the extracellular fluid depots and this means loss of water as well.

The problem of calcium excretion is as important to the student of stones as

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[10] Dock, W.: Kidney. Ann. Rev. Physiol., 9: 225–254, 1947.

[11] Corcoran, A. C. and Page, I. H.: Effects of renin on renal blood flow and glomerular filtration. Am. J. Physiol., 129: 698–702, 1940.

[12] Selye, H. and Stone, H.: Pathogenesis of cardiovascular and renal changes which usually accompany malignant hypertension. J. Urol., 56: 399–419, 1946.

other than excision of the deformed aortic segment could be helpful. Again, hypertension develops in a person with a pheochromocytoma, chiefly because epinephrine increases the flow of blood into the heart; in such an instance, any method designed merely to lower the blood pressure can only be harmful. It is possible that ordinary essential hypertension also represents a compensatory reaction but the inciting disturbance is not yet known. So long as the causative mechanism operates, hypertension will not only persist but will intensify until ultimately the entire organism is destroyed. If a motorist is mired deeply enough in mud, a towcar may, with the best of intentions, jerk the bumper entirely off without affecting the fundamental problem in the least.

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The problem of calcium excretion is as important to the student of stones as it is to the student of bones. This audience need not be reminded that there are four common causes of hypercalciuria.[13] 1) Some of you will remember the important paper that Flocks[14] read before this society 11 years ago in which he showed for the first time, I think, what a high proportion of patients with renal stones excrete calcium in excessive amounts. The cause of this condition is unknown but it differs importantly from that associated with acidosis because it is not affected by alkali therapy. 2) The acute hypercalcemia which sometimes appears when a vigorous young patient is immobilized for orthopedic reasons need not be dwelt on here, and 3) hyperparathyroidism generally offers no diagnostic difficulties. 4) Renal acidosis, however, deserves some comment because it is so frequently overlooked and because therapy is specific and often dramatic.

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[10] Dock, W.: Kidney. Ann. Rev. Physiol., 9: 225–254, 1947.

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"Osteo-nephropathy" is a convenient term which Rule and Grollman[15] suggest be employed to describe the skeletal changes resulting from renal insufficiency of one sort or another. Their classification may perhaps be modified as follows:

Classification of Osteonephropathies

I. Due to renal disease
    1) Tubular dysfunction
        a) Chloride acidosis
        b) Fanconi syndrome
    2) Glomerular insufficiency
II. Due to extrarenal disease
    1) Hyperparathyroidism
    2) Cystine storage disease

All these conditions are rare but that type of tubular disease which results in hyperchloremic acidosis and osteomalacia is worth considering in some detail. This is a functional or chemical disorder because the kidneys are often microscopically normal, the urinary sediment is frequently not remarkable, uremia does not occur, and the usual renal function tests yield normal results. For reasons that are probably enzymatic in nature, the tubules are unable to form an acid urine and to make ammonia[13] so base is lost. Calcium is one such substance and its high concentration in the urine promotes both calculous formation and hypocalcemia. The Albrightian theory then holds that the low serum calcium evokes a homeostatic response on the part of the parathyroid glands which enlarge in an effort to maintain the concentration of calcium in the blood at its usual level; this objective is often achieved but the parathyroid hormone also promotes phosphate excretion and so causes hypophosphatemia. Thus, not only are the bones drained of calcium but recalcification is prevented by virtue of the fact that the proportion of calcium and phosphate ions is inadequate to allow precipitation in osteoid tissue. If the osteomalacia is extensive enough, serum alkaline phosphatase rises. Sometimes, also the loss of potassium is great enough to produce signs and symptoms of hypokalemia. It is not clear why the kidney prefers to reject calcium predominantly or why it reabsorbs chloride in excessive amounts, but the essential laboratory findings which establish the diagnosis are elevation of plasma chloride and diminution of plasma CO_2 combining power.

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[13] Albright, F. and Reifenstein, E. C., Jr.: Parathyroid Glands and Metabolic Bone Disease. Baltimore: Williams and Wilkins Co., 1948.

[14] Flocks, R. H.: Prophylaxis and medical management of calcium urolithiasis; role of quantity and precipitability of urinary calcium. J. Urol., 44: 183–190, 1940.

[15] Rule, C. and Grollman, A.: Osteo-nephropathy; clinical consideration of "renal rickets." Ann. Int. Med., 20: 63–74, 1944.

If too much of the skeleton has not been destroyed, treatment is surprisingly effective. It is designed a) to alleviate the shortage of base and b) to cure the osteomalacia.[13] The fundamental disturbance is corrected by giving enough alkali to relieve the acidosis; the optimum dosage will vary from case to case but it is certainly safe to begin with a daily dosage of 3 to 4 teaspoons of sodium citrate or 50 to 100 cc of Shohl's solution (98 gm. sodium citrate and 140 gm. citric acid per liter of water). Potassium salts are not needed unless specific symptoms of deficiency occur. The second step is based upon the principle that the rate of calcium absorbed from the intestine must be increased if the osteomalacia is to be affected. That is the purpose of the citric acid in Shohl's solution but large amounts of vitamin D must also be given (200,000 units per day may not be excessive), and an adequate amount of calcium in the diet must be assured, artificially if necessary, in the form of dibasic calcium phosphate. Once the osteomalacia is cured these latter measures may be discontinued or the dosages considerably reduced but alkali therapy must be continued indefinitely.

The Fanconi syndrome[16] is another type of tubular dysfunction which causes acidosis and osteomalacia but its essential features (increased excretion of amino acid, lactic acid, glucose and inorganic phosphate) are complicated and poorly understood. Treatment is the same but presumably less effective.

It might be more profitable, I think, to point out how the addition of glomerular insufficiency modifies the picture of tubular acidosis. The patient with uremia due to renal disease (pyelonephritis, glomerulonephritis, polycystic disease, bilateral hydronephrosis) not only loses base in the manner already described but the obliterative lesions of the glomeruli also cause retention of acids. This is reflected chiefly by an increase in plasma phosphate and sulphate, so that the acidosis cannot be easily corrected by giving base. The prognosis is, of course, much poorer, but, even so, the treatment outlined in the preceding paragraphs will do much to repair the osseous disease.

SUMMARY

Attention is drawn to the ability of the kidney to make important homeostatic adjustments. It responds to a failing circulation by reabsorbing excessive amounts of sodium and water. When under stress, it participates in certain endocrinologic adjustments which evoke a rise in arterial blood pressure. Failure of the kidney to excrete acid results in hypercalciuria and skeletal disease.

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[16] McCune, D. J., Mason, H. H. and Clarke, H. T.: Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome). Am. J. Dis. Child., 65: 81–146, 1943.

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HERNIA OF THE KIDNEY

HERMAN L. KRETSCHMER

Lumbar hernia occurs infrequently and a lumbar hernia containing the kidney is extremely rare. Since Ciaccio's article on lumbar renal hernia appeared in 1924, the *Quarterly Cumulative Index Medicus* has not listed this condition. The standard textbooks on urology and general surgery either do not mention the condition or merely state that the kidney may be found in a lumbar hernia.

Plenck in 1774 reported a congenital hernia of the kidney. Monro in 1811 saw a case of bilateral congenital lumbar hernia with the kidneys entirely within the sac, in an infant 6 months old. Bayer in 1888 observed a case in which the contents of the sac consisted of the small intestine, the ascending colon and the right kidney. Ciaccio in 1924 reported a case of right congenital lumbar hernia containing kidney in a child, 18 months old.

Because of the extreme rarity of this condition, and in order to determine the experiences of other urologists, letters were sent to members of the American Urological Association. Two hundred and twenty-eight replied that they had never seen a case of hernia of the kidney. Replies were received from 12 urologists who stated that they had had a case of lumbar renal hernia under their observation. Their case histories are appended to this paper.

Lumbar hernia may occur following kidney operations when the wound closure has been faulty, when primary healing is delayed, after operations for suppurative diseases of the kidney, operations for tumor or kidney stone.

An operation upon the kidney is usually followed by severe fibrosis and adhesions. A subsequent operation upon the kidney is generally very difficult because of the fixation of the kidney to its fossa by adhesions and perirenal fibrosis.

In the case about to be reported, instead of fixation of the kidney following a previous operation for a movable kidney many years ago, the opposite condition was present, namely, great mobility of the kidney so that the kidney was easily palpable in the lumbar hernia. The operation was followed by suppuration for 13 weeks. The patient subsequently developed a hernia in which the kidney was easily palpable (fig. 1).

Because of the rarity of this condition, I wish to report the following case which was referred to me by the late Dr. D. P. Abbott:

Mrs. S. W. was first admitted to the Presbyterian Hospital September 27, 1921 for the treatment of a dislocation of the articular surface of the head of the radius. The patient stated that following the birth of a child in 1893 she had noted attacks of "bladder trouble." In November 1902, while visiting in Chicago, she stooped to lift a suitcase and felt a sudden severe pain in the right lower quadrant. Following the attack of pain, the patient developed frequent and painful urination. The urine was scanty and contained pus and blood. A cystoscopic examination at that time revealed marked cystitis. A right nephropexy was performed at the Baptist Hospital in Chicago on December 12, 1902. "*Drainage*

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

tubes were left in the wound for 13 weeks. She ran a long febrile course following the operation."

Examination on September 27, 1921 revealed a right lumbar hernia, which she stated had been present since her nephropexy. The kidney was easily palpable in the hernial swelling and was very tender upon very careful palpation.

The second admission was November 17, 1921 for the removal of the head of the radius.

Between her second admission on November 17, 1921 and December 2, 1935, she had 21 admissions for the treatment of the following conditions: spastic colitis, ethmoiditis, psychasthenia, arteriosclerosis, conjunctivitis, pernicious anemia, bronchitis, lumbar hernia, and an operation for an acute gangrenous appendix.

The twenty-third admission was December 2, 1935. Two months prior to this admission she was awakened out of a sound sleep by pain over the bladder with an urgent desire to urinate. She had frequency, associated burning, and pain at the end of micturition.

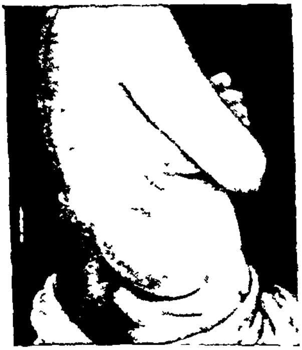

FIG. 1. Lumbar hernia. Kidney palpable under skin. Palpation painful.

During the past summer she reached up high to catch a curtain pole dropped by her sister hanging curtains. A severe pain lasting 3 days developed in the right kidney region. The pain was relieved by lying on the right side.

On another occasion she reached high up to a shelf in the pantry; this precipitated another severe attack of pain in right kidney region with soreness in the area for a couple of days.

She stated that when she stooped to pick up something from the floor she would have pain in right kidney region.

Physical examination revealed a right lumbar hernia, which she stated had been present since the nephropexy in 1921. The kidney was easily palpable in the hernial swelling and was very tender and painful on very careful palpation.

Repeated examinations of the urine showed blood, pus and albumin.

Cystoscopic examination on December 3, 1935 revealed a generalized trabeculation. The left pyelogram was normal. The right pyelogram revealed the kidney pelvis opposite the third lumbar vertebra lying in the "lateral" portion of the abdomen. The ureter ran transversely mesially, then turned downward. Calyces appeared rather broad; otherwise renal pelvis was normal.

Diagnosis: Postoperative lumbar hernia which contains the right kidney (postoperative nephropexy scar).

The twenty-fourth admission was January 22, 1936. The patient complained of many attacks of very severe pain in the right kidney region with considerable distress in this region especially during diarrheal attacks. She was greatly incapacitated following these attacks.

Because of the increasing frequency and severity of her attacks of pain in the kidney, recurring attacks of hematuria, the failure of mechanical supports, and the increasing inability to carry out her usual duties, she was advised to be operated upon.

Operation (February 1, 1936): Because of the marked relaxation of the abdominal wall, the age of the patient (68), the failure of a previous nephropexy, and after due consultation with Drs. D. P. Abbott and William Kirby, it was decided to do a nephrectomy. The old scar was excised. There was a marked bulging of the abdominal wall at the site of her previous nephropexy.

Pathological report: The cortex was normal. The walls of the calyces and pelvis were very thin and showed numerous areas of intramural hemorrhage. Microscopic examination showed several cysts; glomeruli were atrophic and a few were sclerotic. The cellular markings and nuclei of many of the collecting tubules were lost. In several places below the capsule there were areas of round cell infiltration.

Postoperative record: The patient made a smooth and uneventful convalescence. She stayed in the hospital 54 days after the operation for the treatment of colitis, pernicious anemia, sinusitis, and arthritis.

There were 18 subsequent admissions for the treatment of arteriosclerosis, senile dementia, coronary artery disease, chronic pyelitis, spastic colitis, and accidental injuries incurred in falls, and the presence of her lumbar hernia.

She has had no more attacks of pain in the renal area.

The patient died September 1949, of arteriosclerotic heart disease at the age of 81.

In response to letters sent to members of the American Urological Association the following replies were received:

Dr. C. D. Brunkow (Newark, N. J.) had the following experience: Female, 51. Ten years previously she had had two operations for kidney stone performed by another doctor. On physical examination Dr. Brunkow was able to palpate the kidney in the lumbar hernia. He was able to disembed the kidney from the hernia. On coughing, or straining in the erect position, one could feel the kidney slip back into the hernia. Diagnosis was verified by pyelography. She died following an operation for fibroid tumor of the uterus.

Dr. George F. Cahill (New York, N. Y.) replied: "Several years ago we had a patient who had a hernia in the wound and the kidney in the hernia as shown by both intravenous and retrograde pyelograms. He refused to have it corrected, so nothing was done about it."

Dr. Earl E. Ewert (Boston, Mass.) stated as follows: "There is, over at Cook County Hospital, the record of a herniation of the kidney through Petit's triangle; this was a congenital hernia, when I was on Ward 23 in 1927 or 1928. The patient could pop the kidney out through Petit's triangle by lateral flexion and extension of the body and the kidney could be palpated and the vessels felt underneath the skin. Like a lot of other people, I neglected to report this case of a congenital hernia of the kidney through Petit's triangle, and I don't suppose I will ever see another one such as this."

Dr. George M. Fister (Ogden, Utah) mentioned the following case: "I have seen only one patient, in connection with Dr. Dumke, of a female, 45 years of age, with a right lumbar hernia following a kidney operation, in which the hernia apparently contained the kidney. We were definitely able to palpate the kidney in the hernial sac. I have not been able to follow it up."

Dr. Albert E. Goldstein (Baltimore, Md.) had a unique experience. He stated: "Peculiarly enough, two days ago I experienced the first one. Furthermore, it is a bilateral type of hernia of the kidneys. The story is as follows: My procedure for polycystic kidneys had been performed on this individual about eight and four months ago. One side was done by me and the other by a resident. The idea of the procedure is to deliver the polycystic kidney, aspirate as many cysts as possible and then split the kidney lengthwise. The halves of the split kidney are then sutured to the skin hoping to keep them there so that further aspiration can be made. The kidney then remains attached to the skin and always is slightly bulging. In this particular case the right kidney has not remained attached to the skin but kept on protruding out into the lumbar area. This kidney can be pushed back into the renal fossa and held in place by manipulation. The right kidney has herniated the same as the left but not quite as extensive."

Dr Leon Herman (Philadelphia, Pa.) had an extremely unusual type of renal hernia. He wrote that he had seen one patient with a lumbar hernia in which the entire kidney, occupying the sac, could be palpated outside the normal line of the body. Strangely enough this followed an accident in which the patient had been gored by a bull in childhood. The hernia was easily reducible and was held by a bandage so that he did not think operation was necessary.

Dr. Leon Howard (Denver, Colo.) wrote as follows: "I remember distinctly a few years ago having to go and take a kidney out that the patient said another doctor had operated on, and made an incision through the skin and cut the kidney half in two before I got to the muscle. Apparently, there wasn't any hernia, though; it was just a kidney from the looks of it, which had been sewn into the muscle incision as a fixation operation. That is the nearest I could say that I had come to ever seeing a hernia with a kidney in it."

Dr. H. A. R. Kreutzmann (San Francisco, Calif.) reported the following: "The patient, a doctor of medicine, was operated upon by Dr. Kocher of Bern many years ago for a third degree ptosis of the right kidney. Dr. Kocher's technique was to place the kidney in position, leave the wound open, protect it with tampons and thus permit scar tissue to form around the kidney, thereby holding it in place.

"When I examined the doctor in 1943, I could feel a distinct mass bulging from the upper half of the right loin incision. Palpation of the mass revealed a perfectly normal kidney which appeared to be subcutaneous. When this mass was pushed, it shot into the retroperitoneal space and remained there only as long as pressure was kept on the scar. The doctor wears a belt around his middle to keep the kidney in place. Urological examination at that time showed no abnormality of this kidney. The doctor is still living today and is hale and hearty at the age of 82. He still has his kidney."

Dr. P. E. McCown (Indianapolis, Ind.) wrote: "In reply I believe I may say that we have such a case as you specify. This is a patient who has had perinephric abscesses on both sides and has large hydronephrotic sacs in both kidneys with very difficult drainage. In an attempt to repair one side we found the adhesions so great it was impossible to do a proper repair operation, therefore we have installed nephrostomy tubes in both kidneys with which he has been living for about two years. Following this he gained between 40 and 50 pounds in weight and the right wound herniated and contains the kidney."

Dr. Lazarus A. Orkin (New York, N. Y.) answered the inquiry as follows: "I quite agree with you that the ordinary lumbar hernia does not as a general rule contain a kidney. However, about 2 years ago, we had a case on our service at Montefiore Hospital for Chronic Diseases in New York which had had a right nephropexy for a nephroptotic kidney at another hospital some 3-4 years before she came to Montefiore. At the time we saw her, she complained of excruciating pain in the right loin. Examination revealed a large right lumbar hernia and that the kidney was subcutaneous. It is quite interesting that every time she had an attack of severe right loin pain simulating the so-called Dietl's crisis, the kidney could easily be felt displaced subcutaneously. The pain was relieved by having her go to bed and gently manipulating the kidney back to position. The kidney itself was quite hydronephrotic and excretory pyelograms showed a marked angulated and tortuous ureteropelvic junction.

"Because of the fact that she had this marked pain and because she was well on in years, a right nephrectomy was performed and at the time of operation, the pedicle was about 3-3½ in. long. The kidney was found to be subcutaneous. Following the nephrectomy, repair of the lumbar hernia was easily performed.

"This is the only case that I have seen similar to the one that you described."

Dr. R. Pearse (Toronto, Canada) reports the following case: "The patient, a male, had a right pyelolithotomy for stone (elsewhere) followed by a lumbar hernia. Attempted repair was made."

Cystoscopy and pyelography by Dr. Pearse when he first saw the patient showed the colon next to the skin and in the hernial sac, marked lateral displacement of the kidney with hydronephrosis.

At operation the colon and kidney were found just under the skin with a thin layer of fascia covering them. There was obstruction to the pelvis by adhesions. They were removed. The hernia was repaired. The kidney was not removed.

Two weeks after discharge he developed some perirenal urinary extravasation due to obstruction of his ureter and a nephrectomy was done. It was then impossible to repair the hernia."

Dr. Ralph E. Powell (Montreal, Canada) writes: "I have been unfortunate in having two postoperative hernias following nephrectomy. One had a definite mass resembling kidney. Patient refused to have a repair and is deceased."

SUMMARY

A case of true lumbar renal hernia is reported. A careful review of the literature reveals this condition to be very rare. In 11 of the 13 cases reported in this paper, the patients had had a previous kidney operation. In the remaining 2 cases, one was apparently a true congenital renal hernia through Petit's triangle and the other case was the aftermath of goring by a bull.

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REFERENCES

Bayer, K.: Centralbl. f. Chir. 15: 686–688, 1888.
Ciaccio: Policlinico, sez. Chir., 31: 523–540, 1924.
Monro, A.: The Morbid Anatomy of the Human Gullet, Stomach and Intestines. Edinburgh; G. Ramsay & Co., 1811, p. 379.
Plenck, J. J.: Lehrsätze der praktischen Wundarzneywissenschaft. Wien, 1774, J. Grasser, pt. 1, p. 245.

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TREATMENT OF WILMS' TUMOR

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The origin, histopathologic and clinical aspects of adenomyosarcoma or Wilms' tumor are still subject to controversial opinion. Clinicians have been intrigued by the prodigious qualities of these tumors, complex histologic structure, high mortality rate and proclivity for infants and young children.

In 1828, Gairdner presented the first case of renal sarcoma in an infant. These neoplasms were considered carcinomatous in nature until 1870, when Cotanni discovered sarcomatous elements. Two years later Eberth gave the first accurate description of a mixed tumor of the kidney and suggested that it had its origin in remnants of the wolffian body. In 1884, Birch-Hirschfeld stated that the common characteristic was the occurrence of more than one type of tissue, tubual and connective, both embryonal in character. He was the first to use the term "embryonal adenomyosarcoma of kidney". Since the publication of his three-volume monograph, in 1899, covering the structure of these comparatively rare and highly malignant renal mixed tumors, Wilms' name has been closely associated with these neoplasms.

Many theories have been advanced regarding its histogenesis; origin from aberrant germ plasma, rests of the wolffian body, stray cells from myotome or sclerotoma, from renal blastema or nephrotome, cells from embryonic structure of the true kidney which became metamorphosed into cellular structures of various kinds. Ewing's concept of origin from renal blastema is the most widely accepted, though he concluded that no single source of these anomalies should be assumed to exist. Today the controversy among clinicians is relative to the most efficacious treatment of these renal embryonal mixed tumors, whether it be nephrectomy only or a combination or radiation therapy and surgery.

These tumors are difficult to classify pathologically because of the varied histologic findings. The predominating malignant tissues are anaplastic round cells and fairly well differentiated epithelial cells. Microscopically, the most characteristic cell is a mesodermal fibroblast, which may differentiate into renal tubules or glandular structures. The pathological diagnosis depends primarily on finding glandular and stromal cells in a more or less characteristic mixed tumor arrangement. These embryonal growths have been described as adenosarcoma, embryonal sarcoma, myxosarcoma, chondromyosarcoma, rhabdosarcoma, liposarcoma, and Wilms' tumor, which the Standard Nomenclature of Diseases classifies as embryonal carcinosarcoma of the kidney. No fine distinction can be made between the so-called Wilms' tumors and some of the other embryonal renal neoplasms. Kretschmer states that if complete histological studies were carried out on these tumors all the characteristic cell types would be found.

A survey of the literature, particularly of the past decade, indicates no acceptable uniformity of procedure of treatment. Conflicting initial concepts of

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therapy on the part of the referring physician may be contrary to the judgment of the surgeon. I have been asked on occasion to treat a Wilms' tumor as a surgical emergency, and my hospital associates frequently press me with the demand for an opinion as to what constitutes the best chance for cure of malignant renal neoplasms in children. Therefore, I shall review some of the salient features and record my impressions of our present day armamentaria.

In 1887, Jessop performed the first successful nephrectomy for a Wilms' tumor; the child died of recurrence 9 months later. Radiation therapy, as an adjunct to surgery, was introduced in the early part of the century. There is no unanimity of opinion as to which of the following is the preferable form of treatment: 1) nephrectomy only, 2) nephrectomy and postoperative radiation, 3) preoperative radiation and nephrectomy, 4) preoperative radiation, nephrectomy and postoperative radiation, 5) radiation only.

Dean and Barringer have treated Wilms' tumor by radiotherapy alone with favorable results, though Dean states, "this form of treatment is not recommended because in even the most radiosensitive cases it probably requires many months to completely devitalize the tumor and during this time metastases can take place."

Ladd and White obtained the best results by nephrectomy only, and credit their success to the use of the transperitoneal approach with early ligation of the renal pedicle. Hazzard, Melicow and Seidel favor transperitoneal nephrectomy and postoperative radiation, as they believe that the waiting period for the administration of preoperative radiation needlessly jeopardizes the possibility of survival.

There are many advocates for preoperative and postoperative radiation as the patient receives benefits from both forms of therapy. Preoperative radiation shrinks the huge tumor mass and minimizes the dissemination of the malignant cells. Paterson believes that radiotherapy preceding nephrectomy offers greater certitude for obtaining a cure.

Once diagnosis is established, I believe little time is lost waiting from 4 to 6 weeks for the effects of radiation to take place before instituting surgery, and I am convinced that the good accomplished far outweighs the concept that metastases may develop during this interim. As a matter of fact, just when metastases occurs is a moot question. I look upon radiation, not as a cure, but as a procedure, much as iodine is used preparatory to thyroid surgery. It has been demonstrated that even after intensive radiation nests of active malignant cells always remain. The shrinking and avascularity of the tumor which follow radiation greatly reduce the difficulties of extirpation, and I am sure opposes the freeing of malignant cells into the blood stream. The usual encapsulation of this type of tumor favors localization, and, of course, obscures the subjective symptoms. Dean and Pack believe that a firm, solid tumor offers a better prognosis as it remains longer within the capsule.

The material for this survey was compiled from the case histories of Wilms' tumors for the past 20 years at the Children's Hospital, Los Angeles, and my private practice. Only the more pertinent facts relative to treatment and longevity will be stressed. The results of the small number of patients I have to report are, of course, presumptive but still subject to conjecture.

It has been repeatedly stated that there is nothing in the gross and microscopic appearance of the tumor that has any bearing on the prognosis. Is this observation subject to a provision, or, is it an empirical statement based on careful follow-up study? Dickey and Chandler believe that calcification in the tumor is probably a good prognostic sign, as this element was found in their three cases that may be classified as cured.

Of the 40 patients in my study, 28 or 70 per cent are dead; 5 or 12.5 per cent have lived longer than 10 years and may be considered cured; 7 or 17.5 per cent have lived less than 5 years (fig. 1). These measurements were computed from time of diagnosis.

Ladd and White concluded that if a patient survives 2 years after nephrectomy, without evidence of recurrence, it is reasonable to consider the condition cured. In reviewing the literature, and from the course of the disease in 3 of my cases, patients may survive 2 years or longer and subsequently die of recurrence or metastases. One of my patients died 41 months after nephrectomy; though he had an uneventful course 3 months prior to death. One child, 9½ years of age, showed no evidence of recurrence for 26 months, and death occurred 5 months later. Another child died 33 months subsequent to nephrectomy. Abbe's patient lived 4 years, 7 months, and then died of metastases. Recently, Ritter and Scott reported the occurrence of an embryoma of contralateral kidney 10 years following nephrectomy for Wilms' tumor.

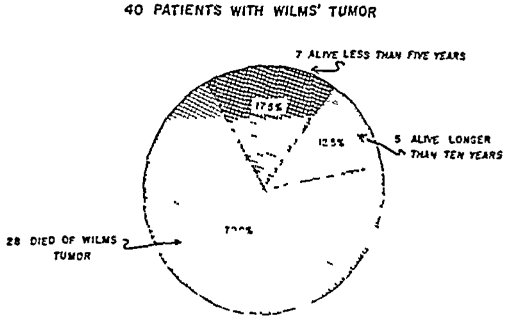

FIG. 1

The diagnosis of the 34 nephrectomized patients was confirmed by histopathological examinations. The diagnosis was established in 1 case by clinical and roentgenographic examinations. Postmortem microscopic examinations were done on 5 cases.

The 2 cases that received no treatment showed evidence of metastatic lesions at the time of diagnosis, and death occurred within 1 month and 1½ months respectively. One of the autopsies revealed the most extensive metastases the pathologist had ever encountered.

The clinical diagnosis in 1 case was confirmed by biopsy of a node in the inguinal region. No therapy was administered in view of the extensive metastases, and the child died within 2 months.

The 12 children who are still alive received radiation therapy in combination with nephrectomy. See table 1.

The group of living patients all received radiation therapy as an adjunct to nephrectomy; 17.9 per cent of the deceased group did not receive radiation therapy. Of the children living, 41.7 per cent received radiation prior to operative interference, and only 28.6 per cent of the deceased group were so treated. See figure 2.

The vast majority of cases of embryonal developmental mixed tumors of the kidney, or so-called Wilms' tumor, occur prior to the tenth year of life; though 56 cases have been reported in adults and Clay reported a case of a patient 80 years of age. Necropsy examination on a 7 month fetus revealed the presence of a Wilms' tumor. Silver is credited with having treated the youngest patient, an infant 3 days old, who received preoperative radiation, and at the time he reported the case the child was 4½ years of age.

TABLE 1. *Types of therapy administered to 40 patients with Wilms' tumor*

	DIED OF WILMS' TUMOR	ALIVE LESS THAN 5 YEARS	ALIVE LONGER THAN 10 YEARS	TOTAL
Nephrectomy only	2	—	—	2
Nephrectomy and postoperative radiation	12	5	2	19
Preoperative radiation and nephrectomy	3	—	2	5
Preoperative radiation, nephrectomy and postoperative radiation	5	2	1	8
Radiation only	3	—	—	3
Biopsy	1	—	—	1
Not treated	2	—	—	2
Totals	28	7	5	40

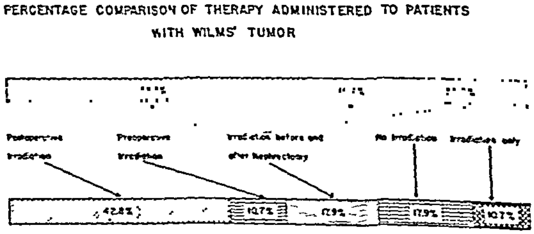

FIG. 2

In my survey the age distribution was between 3 months and 10 years, with 60 per cent of the cases occurring before the third year of life (fig. 3). From some theories of the histogenesis of these tumors, the inclusion of various embryonal tissues, the age of the child at the time of diagnosis has been closely related to prognosis, the assumption being that the older the child the longer has the neoplastic lesion been present, enhancing the possibilities for growth extension and metastases. The 5 patients in my group who may be classified as cured were aged: 6 months, 2½ years, 3 years, 5 years and 5½ years.

Hazzard, Melicow and Seidel believe that prognosis is influenced by age, as the younger the patient, the more easily the tumor is felt, resulting in early diagnosis and treatment.

The sex incidence in this group was: 21 males and 19 females (fig. 4). The left kidney was involved more often than the right; left 24 times and the right 15 times. In 1 case there was bilateral involvement.

The bilateral Wilms' tumor was diagnosed as polycystic kidneys by excretory pyelograms, and the neoplastic condition was demonstrated when a left nephrectomy was performed. Radiation therapy of 1400r was administered to the right side subsequent to the left nephrectomy. The massively enlarged right kidney showed marked decrease in size following therapy. The child was in good general condition 6 months postoperatively. While bilateral involvement is rare, there is always the question whether the neoplasm on one side represents secondary invasion from an initial unilateral lesion.

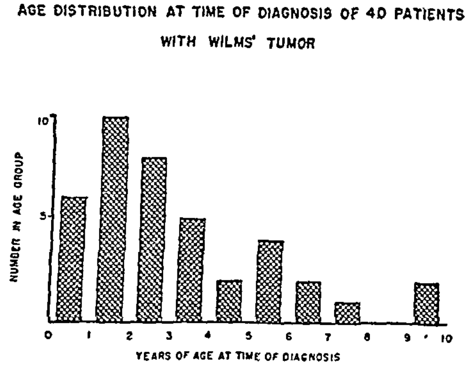

FIG. 3

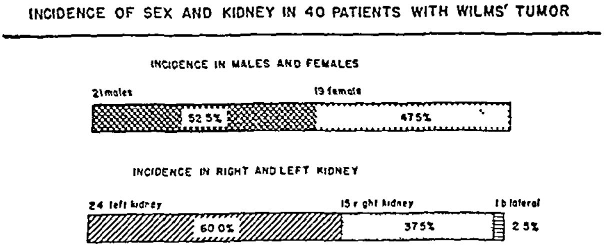

FIG. 4

The autopsy in 1 case revealed secondary invasion of tumor tissue about the opposite kidney with no involvement of that kidney. In 1897, Walker reported 10 bilateral cases, though since the turn of the century there has been a marked decrease in this phenomenon.

Familial tendency has been reported by Maslow. He observed 3 occurrences in one family; 1 brother and 2 sisters. Chapian treated 2 brothers.

SYMPTOMATOLOGY

Inasmuch as some clinicians believe that the tumor is congenital in nature, no appropriate time element can be selected for onset of symptoms. Portent signs are indiscernible until a large abdominal mass presents itself. How long the tumor has been growing is conjectural. In some cases the child will present a very large abdominal tumor a few days following a complete physical examination. There is a great similarity of symptoms, but a wide variation of the structural aspects of the tumor itself.

In my group, the interval for the duration of symptoms was from 1 day to 18 months. There appears to be no correlation between the length of time symptoms are observed prior to treatment and prognosis. In 1 case, the mother had noticed an enlargement of the infant's abdomen for 4 months before obtaining medical advice. The child is alive and well 13 years subsequent to nephrectomy. In another child the tumor mass was discovered following a fall; medical attention was administered immediately and the child is alive and well 12 years postoperatively. Observance of the tumor in another child was of 1 day's duration and death occurred within 2 months. A child who had an enlargement of the abdomen for 18 months prior to diagnosis died 7 months later.

Embryonal mixed tumors of the kidney have an insidious onset but are relentless in their course. The rapid progression of the lesion, following the presence of the tumor mass, is accompanied by malaise, weight loss, fever and pain.

The absence of hematuria has been attributed to the encapsulation of the neoplasm. Nevertheless, hematuria was the initial symptom in 3 of my cases. One child received a course of radiation with accompanying decrease in the size of the tumor, but the child's general condition did not warrant a nephrectomy and he died 1 month after treatment was instituted. At autopsy, the histopathological examination showed the tumor to be surrounded by a thin capsule which appeared intact. In 1 case where hematuria was present there was also severe pain about the umbilicus, and the histopathologic report stated: "The tumor itself is moderately soft, very friable, varies from a grayish white to brick red color and contains many large blood clots. The kidney capsule is thickened and when stripped leaves a pale smooth finely granular surface showing small petechial hemorrhages." This child received radiation, preoperatively and postoperatively, and died within 31 months. The other child, who had hematuria as the initial symptom, received radiation before and after nephrectomy and is alive 14 months subsequently without evidence of recurrence or metastases.

DIFFERENTIAL DIAGNOSIS

I believe that pyelographic studies should be done routinely on all children with an abdominal tumor mass. The most likely diagnosis in a child under 5 years of age with such a condition is an embryonal mixed tumor of the kidney, and diagnosis should be established by pyelography prior to operative interference. An excretory urogram demonstrating a functionless kidney in the presence of an abdominal mass more frequently represents hydronephrosis and emphasizes the importance of retrograde pyelography to confirm the diagnosis of tumor. The differential clinical diagnosis could be hydronephrosis, adrenal neuroblastomas, pyonephrosis, congenital polycystic kidneys or hypernephroma.

Pyelograms were done in 33 cases of my group; 23 excretory urograms, 5 retrograde, and 5 both excretory and retrograde pyelograms. In 4 cases the pyelographic studies were not done until the tentative diagnosis could no longer be confirmed. This procedure established the diagnosis in all cases except the child who had bilateral Wilms' tumors, and these excretory urograms were interpreted to be polycystic kidneys.

The cardinal symptom in 2 cases was severe abdominal pain. One child, on whom no pyelographic study was done, was operated on for what was thought to be a ruptured appendix, at which time the renal neoplasm was diagnosed. The other child, also conservatively treated for what was considered a ruptured appendix, continued to have symptoms, whereupon pyelograms were done; these established the presence of a kidney tumor. Two children were treated for splenic involvement: one was thought to have a splenic tumor, and the other a rupture of the spleen, as the discovery of the mass was associated with trauma.

No large group of patients has received the same treatment, and until more statistical data are available I believe it would be fallacious to credit any one factor, be it type of nephrectomy, radiation only, or in combination with surgery, as giving the best prognosis. It is a truism that prognosis is dependent on recurrence and metastases, and why these factors remain in a quiescent state in a few cases is indeterminate.

TABLE 2. *Group of living patients with Wilms' tumor who may be classified as cured*

AGE AT TIME OF DIAGNOSIS	NEPHRECTOMY	PRE-OPERATIVE RADIATION	POSTOPERATIVE RADIATION	YEARS SINCE DIAGNOSIS
65 months	Posterolumbar	2,800r	—	12
60 months	Posterolumbar	3,000r	2,800r	13 (Full-term pregnancy)
6 months	Posterolumbar	2,000r	—	13
29 months	Transperitoneal	—	5,640r (Renal area) 4,500r (Metastatic lesion)	15
36 months	Posterolumbar	—	1,200r	20 (Full-term pregnancy)

I favor radiation as an adjunct to nephrectomy, and my 5 patients who may be classified as cured, each received this method of treatment (table 2). Posterolumbar nephrectomies were performed on 4 children, and 1 child had a transperitoneal nephrectomy. Available data are insufficient to permit the evaluation of the merits of these surgical procedures. The 2 patients who have each had one full-term pregnancy had uneventful courses of gestation. Seven years ago the patient who has lived 15 years from time of diagnosis, developed a metastatic lesion at the end of the eleventh rib. Roentgen rays totaling 4500r were administered with regression of the lesion, and to date there has been no recurrence, which is most uncommon. Kerr reported a case with pulmonary metastases which disappeared following radiation.

The microscopic findings of 2 cases showed the tumor mass well encapsulated. The pathological findings in another case stated the tumor was very firm in consistency and well circumscribed. In still another case the tumor was round and slightly nodular. The histopathological finding of another case was a thin, fibrous capsule with a light yellow central portion.

In the child, who was 6 months of age at time of diagnosis, the operative findings revealed a fairly normal-sized and normal appearing kidney except for the anterior upper half which was made up of the shrunken wrinkled mass of tumor now reduced to practically nothing; and at one place the tumor had invaded the peritoneum. This child is alive and well, 13 years after treatment, without evidence of recurrence.

Within the past year 5 of these 7 patients have been operated on and the prognosis is problematical. All of these children received radiation in combination with nephrectomy (table 3).

The child who has lived 55 months since receiving preoperative and postoperative radiation, has never shown any evidence of recurrence or metastases. The histopathological examination showed the tumor to be encapsulated.

The child who was 5½ years of age at the time of diagnosis, and is alive 9 months subsequently, has a bizarre history. When first examined at 10½ months of age, he was a fully developed male with large genitalia, hairy body and increased secretion of 17-ketosteroids. The operative findings showed a right suprarenal gland many times enlarged, about 3 cm. in diameter, firm and greyish-yellow in color. The entire intestinal tract, from stomach downward, felt and appeared normal, as did the gallbladder, liver and spleen. The left suprarenal gland and both kidneys felt normal. The histopathological report stated:

TABLE 3. *Group of living patients with Wilms' tumor who may not be classified as cured*

AGE AT TIME OF DIAGNOSIS	NEPHRECTOMY	PREOPERATIVE RADIATION	POSTOPERATIVE RADIATION	NUMBER OF MONTHS SINCE DIAGNOSIS
mos.				
120	Transperitoneal		3000r	5
22	Posterolumbar, left Radiation, right		1400r	6
14	Posterolumbar		3000r	7
65	Transperitoneal		3000r	9
23	Transperitoneal		3000r	10
7	Transperitoneal	2000r	3600r	14
12	Transperitoneal	300r	3000r	55

"Section of the adrenal tumor shows a relatively uniform structure throughout. It appears to be encapsulated on three sides. The tumor itself consists of cords of cells which resemble cortical cells. They bear the closest resemblance to the zona reticularis of the adrenal, although at one point there are some pseudoglomerular formations which are consistent with derivation from the glomerular zones of the cortex. The cells for the most part are large and pale with stippled vesicular nuclei. Scattered here and there are considerably larger cells; some of which have the nuclei pushed over toward the margin. These cells have a honey appearance. Occasional cells are noted which contain several nuclei. These are infrequent and there is some question as to whether or not they represent several cells which are closely packed together so that cytoplasm appears to blend. At one point in the margin of the tumor, there is, *outside of* the fibrous capsule which seems to surround the tumor, some adrenal tissue which looks like the outer cortical layer, although it is somewhat compressed. This is distinctly separated from the main body of the tumor. The fat stain shows large numbers of cells containing large red fat droplets. The foamy appearing cells, in particular, contain the largest quantities, but almost every cell in the section contains some fat. Diagnosis: Tumor of adrenal cortex."

Following the excision of the right suprarenal gland, the genitalia decreased in size and the patient resumed the characteristics of a normal child. When 19 months old, he was found to have a left hemihypertrophy, at which time the 17-ketosteroids were normal. Periodic physical examinations were made and no abdominal findings were noted until April 1949, when a large mass was felt in the abdomen. The child had complained of occasional abdominal pain around the umbilicus and infrequent episodes of constipation. The physical examination showed a well-healed right upper quadrant scar. There was a large movable mass which was moderately firm, nontender, in the right lower quadrant extending across midline and above the umbilicus. Examination of the genitalia revealed a large penis with some light hair around the genitalia. The testicles were descended and normal in size. Histopathological diagnosis: adenomyosarcoma, region of right kidney with invasion of kidney.

TABLE 4. *Number of months between diagnosis of Wilms' tumor and death*

Number of months	½	1	2	3	4	5	6	7	8	9	12	31	33	41	
Number of patients	1	3	4	2	3	2	2	4	2	1	1	1	1	1	28

Radiation therapy, 3,000r, was administered postoperatively, and 4 months subsequent to nephrectomy there was roentgenographic evidence of pulmonary metastases.

To date 28 children, or 70 per cent of the entire group are dead (table 4). Twenty-five children died within a year, and 60 per cent of the deceased were dead within 6 months. Twenty-two had nephrectomies; 12 posterolumbar and 10 transperitoneal approach. Statistics presented by various authors indicate an ultimate mortality rate of more than 90 per cent.

METASTASES

Metastatic lesions were present in 30 cases, of which 28 are dead. Regression occurred in only 1 case, that of the child who has lived 15 years and may be considered cured. The other child with metastatic lesions is alive, 9 months postoperatively, with an adverse clinical course.

Metastases usually progress by direct infiltration; the most common occurrence being by way of lymphatics or blood stream, though unusual invasive qualities of this tumor have been recorded. Metastases to the bone in embryoma of the kidney is a very rare phenomenon. Osseous metastases were present in 3 of my cases, and only 5 other such cases have been reported.

At the time of diagnosis one of my cases showed roentgenographic evidence of metastatic lesions of right ulna, radius, femur, jaw and axilla. Radiation therapy, amounting to 900r, was administered to the tumor which decreased in size, 750r was given to the metastatic lesions which progressed rapidly, and the child died within 2 months. Another child had metastatic lesions of the skull, facial bones and extremities, and died 2 months following diagnosis. As previously stated, there was regression of a metastatic lesion of the rib in 1 case. Kerr, Dean and Bothe all recommend radiation therapy for metastases.

In 1 case, hematuria, vaginal bleeding and a firm mass in the bladder region occurred 26 months subsequent to nephrectomy, and 5 months later the autopsy showed metastases involving lungs, liver, bladder, uterus and pleura. Metastases to the spermatic cord were present in one instance.

TABLE 5. *Interval between first radiation therapy and nephrectomy on patients who died of Wilms' tumor*

PREOPERATIVE RADIATION	NUMBER OF DAYS BETWEEN FIRST TREATMENT AND NEPHRECTOMY	POSTOPERATIVE RADIATION	NUMBER OF MONTHS LIVED SINCE DIAGNOSIS
1,800r	17	1,500r	31
3,000r	19	3,600r	8
1,500r	27	4,950r	7
3,000r	29	—	41
2,550r	38	—	3
3,000r	48	2,450r	9
1,800r	48	150r	4
3,000r	67	—	4

TABLE 6. *Interval between first radiation therapy and nephrectomy on patients who are living with Wilms' tumor*

PREOPERATIVE RADIATION	NUMBER OF DAYS BETWEEN FIRST TREATMENT AND NEPHRECTOMY	POSTOPERATIVE RADIATION	LENGTH OF TIME LIVED SINCE DIAGNOSIS
300r	6	3,000r	55 months
3,000r	24	2,800r	13 years
2,000r	38	—	13 years
2,000r	42	3,600r	14 months
2,800r	54	—	12 years

I computed the length of time between administration of first roentgen therapy and surgery to see whether this had any effect on prognosis. There is wide variation in this time element, and no accurate conclusions could be interpreted. In table 5 it varies from 2½ to 9½ weeks, and in table 6 from 1 to 8 weeks. The distinguishable characteristic of the 3 who have lived the longest is that they received approximately the same amount of roentgen therapy in proportion to their age. The child who received 2000r was just 6 months of age, and the other 2 children were 5 and 5½ years of age.

It is generally concurred that roentgen therapy is more useful in treating embryonal mixed tumors than in other renal neoplasms. As to nephrectomy following radiotherapy, Schenck, Rowe and Frazer believe that 4 to 6 weeks is the ideal waiting period, whereas Paterson affirms that the interval should be from 6 weeks to 3 months. He states: "After this interval, a nephrectomy is indicated, because, although the main mass of the tumor consists of highly sensitive cells, it seems to contain as well some resistant elements which, if not removed, may eventually give rise to recurrence."

TABLE 7. *Reported survivals of 72 patients with Wilms' tumor*

AUTHOR	NUMBER OF CASES	NEPHRECTOMY ONLY	PREOP. X-RAY AND NEPHRECTOMY	NEPHRECTOMY AND POSTOP. X-RAY	PREOP. X-RAY NEPHRECTOMY AND POSTOP. X-RAY	RADIATION ONLY
Abbe	1	1				
Barringer*	1					1
Coley†	1	1				
Daw	2			1	1	
Dean	5					5
Deming	3	1	2			
Dickey and Chandler† ‡	3				2	1
Gahagan and Yearwood	2			1	1	
Hazzard, Melicow and Seidel	3	3				
Higgins and Shively	4	2	1		1	
Israel	1	1				
Kretschmer	1			1		
Ladd and White	8	7	1			
Lippert	1	1				
Loeb	1			1		
Mandeville and Nelson	1		1			
McNeill	2					2
Mixter	2	2				
Nesbit and Adams	6	2	2	1		1
Ockerblad and Carlson	1			1		
Ritter and Scott§	1	1				
Sauer	1					1
Silver	6	3		2	1	
Van Duzen	1	1				
Wade	1	1				
Weisel, Dockerty and Priestley	5	1		2	2	
White	1	1				
Wollstein	2	2				
Author's	5		2	2	1	
Totals	72	31	9	12	9	11

* Reported case of Sisk.

† Received Coley's vaccine, operated by Perkins.

‡ Case treated by radiation alone, had excision of tumor.

§ Child lived 10 years and then developed Wilms' tumor in opposite kidney.

There are no criteria as to the most beneficial dosage of roentgen rays, as the individual structural variations of these tumors preclude a uniformity of response to roentgen therapy.

These tumors are composed of radiosensitive and radioresistant cells which are not completely destroyed by radiation. We have been unable to fully comprehend the regressive action as a result of this procedure. The clinical observation of reduction in size of the neoplasm is evident by the widespread necrosis of the tumor cells. Bothe, Alcock and others have studied specimens before and after radiation, and found an abundance of stroma but few embryonal cells. They concluded that the malignant embryonal cells are destroyed, though the malignant character remains. It is possible that the dosage may have been inadequate, or surgery was performed before the full effects of the radiotherapy had been established, inasmuch as 11 cases have been reported as cured by treatment with radiation only. An elucidation of this query might possibly be forthcoming by extensive histological examinations of all Wilms' tumors subjected to radiotherapy.

There is no unanimity of opinion as to the number of units to be administered at one time. The majority of the cases in my group received 150r daily. Kerr gives 200r per day, and Paterson advocates a maximum of 90r daily. Dean says if radiation alone is to be used the dosage should be from 75 to 100r. Priestley and Broders recommend radiation therapy every 6 to 8 weeks, for at least 5 or 6 months following surgery, even if there is no evidence of recurrence. There are others who believe that prophylactic radiation for unproved metastases is unwarranted. Sauer reported a patient living 10 years, treated by radiation only, receiving 4,826r. Whereas McNeill's patient, who received the same treatment, living 8 years, received a total of 10,319r.

REPORTED FIVE-YEAR SURVIVALS OF 72 PATIENTS WITH WILMS' TUMOR
RELATIVE TO RADIATION THERAPY

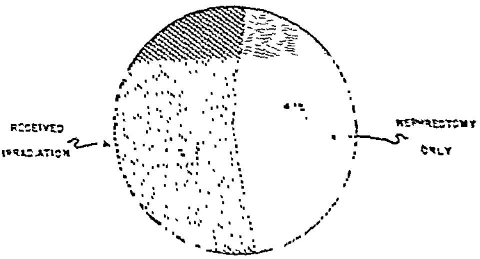

FIG. 5

In 1894 Israel recorded the first cure of a Wilms' tumor in a 14 year old boy. Abbe reported his case in 1912, and since that time I was able to find 65 other reported cures in the literature (table 7).

As shown in figure 5, 57 per cent received roentgen therapy in one form or another, and 43 per cent had no treatment other than nephrectomy. Of the group of 31 who had nephrectomy only, I was unable to estimate with any degree of accuracy which surgical approach had been employed.

Figure 6 shows the percentage of these cures relative to the type of therapy administered: 43 per cent, nephrectomy only; 16 per cent, postoperative radiation; 26 per cent, preoperative radiation, and 13 per cent of this group also received therapy postoperatively; and 15 per cent of these 72 patients were cured by radiation only.

I was able to ascertain the age at time of diagnosis of 54 patients, which ranged from 1 month to 49 years. Of this group, 57 per cent of the occurrences were before the third year of life. Four patients had reached maturity at the time of diagnosis; Israel's patient was 14 years of age; one of Weisel's group was 24 years; one of Silver's 27 years; and Loeb's patient was 49 years of age.

REPORTED FIVE-YEAR SURVIVALS OF 72 PATIENTS WITH WILMS' TUMOR RELATIVE TO TYPE OF THERAPY ADMINISTERED

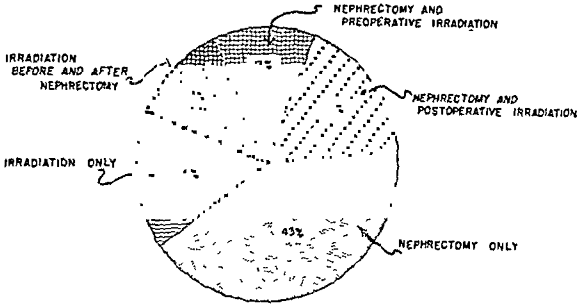

FIG. 6

SUMMARY

Statistical data pertaining to 40 patients with Wilms' tumor, ranging in age from 3 months to 10 years are presented, with one incident of bilateral involvement. A case of the development of Wilms' tumor on corresponding side 4½ years subsequent to removal of adrenal cortex tumor is recorded.

Compilation of reported 5-year survivals relative to type of therapy administered has been made.

No standard treatment was used in the management of these patients. Five patients, who are alive over 10 years, received radiation therapy as an adjunct to nephrectomy; 3 received it preoperatively and 1 also had postoperative radiation. The child who is alive 55 months, without evidence of recurrence, received radiation therapy preoperatively and postoperatively.

The results of this study suggest that radiation therapy should be instituted as soon as the diagnosis of Wilms' tumor is established, and that nephrectomy should be postponed until after such treatment.

Closer cooperation among urologists, radiologists, pediatricians, and/or family doctor would help improve the present day management of Wilms' tumor.

Since most studies and observations suggest an answer but do not prove the issue, and inasmuch as there is considerable confusion in the minds of physicians both within and outside the speciality of urology, would it be amiss to appoint a committee of representative experts to approve the most acceptable plan for the treatment of malignant renal neoplasms in children, consisting of a general surgeon, radiologist and pediatrician.

Since the presentation of the paper, the child who had received preoperative and postoperative radiation, and was reported alive 55 months later without evidence of metastases, may now be classified as a 5-year cure.

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REFERENCES

Abbe, R.: Ann. Surg., 56: 469–473, 1912.
Barringer, B. S.: J. Urol., 38: 1–14, 1937.
Birch-Hirschfeld, F. W. and Doderlein, A.: Centralbl f. d. Krankh. der Harn- und Sexual-Organe, 5: 88–97, 1894.
Bothe, A. E.: U. S. Nav. M. Bull., 40: 892–901, 1942.
Chapian, M. A.: R. I. Med. J., 31: 105–106, 1948.
Clay, J.: Brit. Med. J., 2: 1083, 1930.
Coley, W. R.: Am. J. Surg., 29: 463–464, 1935.
Daw, W. J.: Penn. Med. J., 46: 1293–1295, 1946.
Dean, A. L.: N. Y. State J. Med., 45: 1213–1217, 1945.
Dean, A. L. and Pack, G. T.: J.A.M.A., 98: 10–17, 1932.
Deming, C. L.: J. Urol., 55: 571–582, 1946.
Dickey, L. B. and Chandler, L. R.: Pediatrics, 4: 197–200, 1949.
Eberth, C. J.: Virch. Arch. f. path. anat., 55: 518–520, 1872.
Ewing, J.: Neoplastic Diseases. Philadelphia: W. B. Saunders Co., 1940, p. 814.
Gahagan, H. W. and Yearwood, H. M.: J. Urol., 62: 295–299, 1949.
Gairdner, E.: Edin. Med. & Surg. J., 29: 312–315, 1828.
Hazzard, C. T., Melicow, M. M. and Seidel, R. F.: N. Y. State J. Med., 49: 649–657, 1949.
Higgins, C. C. and Shively, F. L.: Arch. Surg., 42: 386–394, 1941.
Israel, (Arch. f. Chir. 1894) quoted by Walker, G.: Ann. Surg., 26: 529–602, 1897.
Kerr, H. D.: J.A.M.A., 112: 408–411, 1939.
Kretschmer, H. L.: J. Urol., 39: 250–275, 1939.
Ladd, W. E. and White, R. R.: J.A.M.A., 117: 1858–1863, 1941.
Lippert, K. M.: J. S. Carolina Med. Assoc., 65: 39–41, 1949.
Loeb, M. J.: J. Urol., 61: 20–22, 1949.
Mandeville, F. B. and Nelson, C. M.: Urol. & Cut. Rev., 49: 204–208, 1945.
Maslow, L. A.: J. Urol., 43: 75–81, 1940.
McNeill, W. H. (quoted by Mertz, H. O., et al.): J. Urol., 46: 1103–1120, 1941.
Mertz, H. O., Howell, R. D. and Hendricks, J. W.: J. Urol., 46: 1103–1120, 1941.
Mixter, C. G.: Ann. Surg., 96: 1017–1027, 1932.
Nesbit, R. M. and Adams, F. M.: J. Ped., 29: 295–303, 1946.
Ockerblad, N. F. and Carlson, H. E.: J. Urol., 50: 265–267, 1943.
Paterson, R.: Treatment of Malignant Diseases by Radium and X-ray. Baltimore: Williams & Wilkins Co., 1949.
Priestley, J. T. and Broders, A. C.: Proc. Staff Meet. Mayo Cl., 10: 80–84, 1935.
Ritter, J. A. and Scott, E. S.: J. Ped., 34: 753–757, 1949.
Sauer, H. R.: N. Y. State J. Med., 48: 497–500, 1948.
Schenck, S. G.: J. Ped., 33: 734–738, 1948.
Silver, H. K.: J. Ped., 31: 643–650, 1947.
Van Duzen, E.: (quoted by Mertz, H. O., et al.) J. Urol., 46: 1103–1120, 1941.
Wade, H.: Austral. & New Z. J. Surg., 5: 1–17, 1935.
Walker, G.: Ann. Surg., 26: 529–602, 1897.
Weisel, W., Dockerty, M. and Priestley, J.: J. Urol., 50: 399–413, 1943.
White, W. C.: Ann. Surg., 94: 139–142, 1931.
Wollstein, M.: Arch. Path. & Lab. Med., 3: 1–13, 1927.

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NEPHROPEXY

GEORGE R. LIVERMORE

The numerous operations that have been devised for the relief of ptosed kidneys seem to indicate that no one of them is entirely satisfactory.

At the 1925 meeting of the American Urological Association in St. Louis, I attended the clinic of Dr. C. E. Burford. He was demonstrating the Kelly operation for nephropexy which he stated had been very successful in his hands. He operated upon 2 cases, then showed us a post-mortem specimen taken from a woman upon whom he had operated several years previously and who had recently died from pneumonia. The specimen showed the kidney firmly anchored to the twelfth rib.

We know many urologists say the Kelly operation is wrong because it anchors the kidney, which is a movable organ, firmly to the twelfth rib. Regardless of this, and the post-mortem specimen of Dr. Burford proves that this operation does fix the kidney firmly to the twelfth rib, I have found the operation most satisfactory in a series of 52 cases. It is true that some patients will complain of a dull ache in the loin following the operation, but this usually subsides in a few months. In fact, I have not seen a case in which it did not subside in time. In these 52 cases there were 48 women and 4 men. The ptosis occurred on the right in 48 cases; on the left in 4. In women it involved the right kidney in 46 cases, the left in 2; while in men it involved the right in 2 and the left in 2. See figures 1, 2 and 3.

ETIOLOGY

The cause of movable kidney is a disputed question. In lawsuits with a history of blows or falls involving the renal area, the attorney for the plaintiff invariably tries to prove that the injury caused the movable or floating kidney. We urologists know that an injury violent enough to displace a kidney would cause rupture before it caused displacement. It occurs more frequently in women than in men. Southam says it occurs 12 times as frequently and in Bell's series there were 300 cases in women and only 10 in men. Loss of weight and absorption of the perirenal fat are, in my opinion, a frequent cause. We however see movable kidneys in well developed persons. I should say the chief cause of movable kidneys is a violet strain at work or play (especially that which occurs in foot or basket ball) which loosens the kidney slightly from its perirenal fat. At each succeeding strain the motility is gradually increased until finally there is a movable or floating kidney.

SYMPTOMS AND SIGNS

Dull ache or dragging pain in the loin, usually with renal colic at intervals, is the most prominent symptom. In some cases the colic is relieved when the patient lies down. Frequency, burning and nocturia are periodic symptoms. In-

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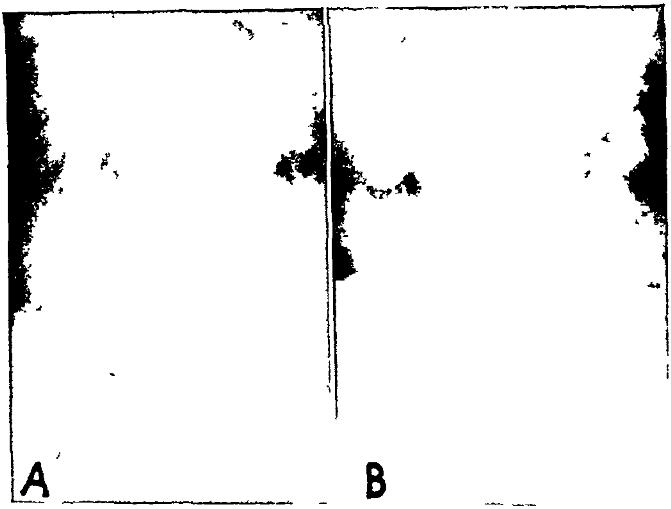
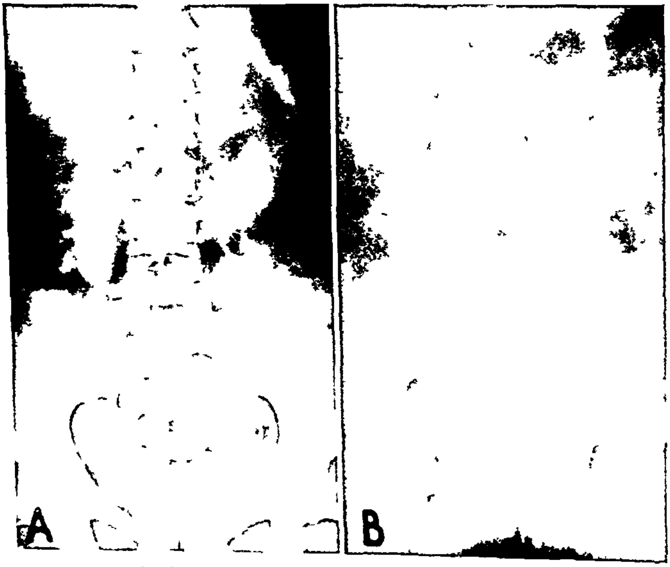
Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May, 24, 1950.

termittent hematuria due to inflammation and congestion of the dilated pelvis and ureter, from back pressure, may be a prominent symptom. Various nervous manifestations, especially in women, are frequent complications. This is attributed to the drag on the kidney pedicle, plus the pain and infection. Pus and red blood cells usually are found in the urine, though cases of long standing often show only a rare leukocyte, which most men consider normal urine.



Before Afterwards

FIG. 1

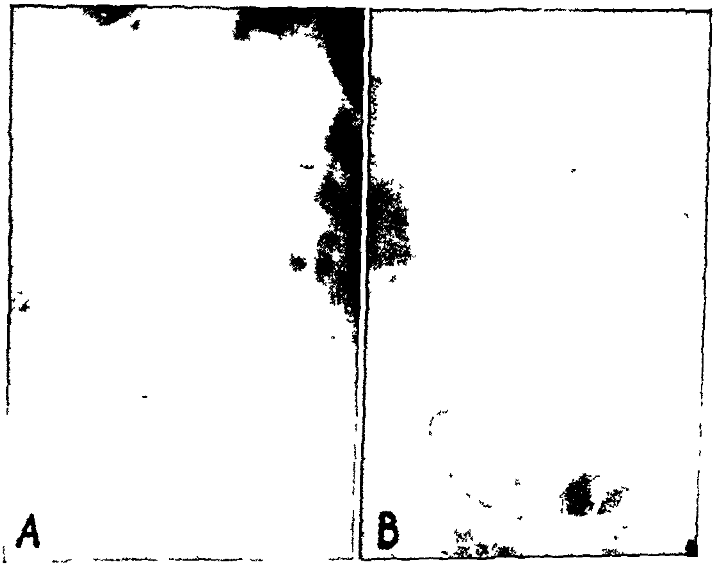


Before Afterwards

FIG 2

TECHNIQUE

Kelly's method, as demonstrated by Burford, anchors the kidney to the twelfth rib, one suture above and one below the rib. The sutures are silk in infected cases and No. 1 chromic catgut in noninfected ones. They are passed through the capsule in a circular manner, the so-called 3 point stitch. We use only one suture of 00 chromic gut and this near the lower pole, owing to the ease with which the suture in the capsule can be torn out; the support of the kidney is reinforced by the Deming operation. It is not necessary to use more than two sutures in doing the Deming operation and usually one is sufficient. We only want this extra support to aid in holding the kidney in position until firm adhesions have formed. I have been so pleased with this operation I now use it almost routinely.



Before

Afterwards

FIG. 3

All cases of nephroptosis should not be subjected to operation. Age is not a contraindication. Elderly people usually weather nephropexy exceptionally well. The physical condition, however, must be very carefully checked and, as in all kidney surgery, a knowledge of the condition and function of the other kidney is a prerequisite. If there are no gross anomalies that we believe cannot be corrected and there is definite evidence that the malposition is damaging the kidney, and infection persists, or the patient suffers pain or colic, or hematuria and dysuria are annoying symptoms, nephropexy should be done. If there is no apparent kidney damage, as demonstrated by a careful urological study, nephropexy should not be done unless a well-fitting kidney corset, suitable medication and elevation of the foot of the bed will not relieve the symptoms.

Burford stresses the point of freeing the ureter of all adhesions, especially about the ureteropelvic junction. This has always been my practice and I deem it most important. Another point he mentions, when the kidney is anchored, the ureter must be straight but never taut. I am in complete accord with this.

Still another point that I wish to bring out: In cases where the ureter has undergone inflammatory elongation and even when the kidney is anchored there is still some redundancy, it is our practice to insert an indwelling ureteral catheter on the third or fourth postoperative day and leave it in position (irrigating every 6 hours with phemerol solution 1:15,000) until the patient is out of bed on the fourteenth day.

I agree wholeheartedly with Burford that all ptosed kidneys should not be subject to nephropexy. All of us older men have seen patients go through life with floating kidneys that could be palpated well below the crest of the ileum and even pushed beyond the midline, which caused few or no symptoms. I am sure the lack of symptoms in such cases is due to the fact that the ureter does not become obstructed.

My rule in the selection of cases for operation is pain, hematuria, kidney damage, persistent infection and, of course, the age and physical condition of the patient. Other kidney surgery does not prevent the performance of nephropexy. Stones can be removed, anomalous vessels ligated and severed, plastic operations on the pelvis and reimplantation of the ureter can be done. In a recent case, I did a heminephrectomy and removed the entire duplicate ureter, then anchored the remaining portion of the kidney with a most satisfactory result.

Many cases in thin people can be successfully treated with a kidney corset and elevation of the foot of the bed. The corset must fit snugly and at the first sign of loosening should be readjusted. The patient, too, should be instructed to eat fattening foods. The corset must be worn at least a year and longer if the kidney remains ptosed.

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REFERENCES

Bell, J. J.: Brit Med. J., **1:** 887, 1923.
Burford, C. E.: J. Urol. **55:** 220, 1946.
Goldstein, H. H.: Urol. & Cutan. Rev., **54:** 136, 1950.
Southam, A. H.: Quart. J. Med., **16:** 283, 1923.

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CROSSED RENAL ECTOPIA WITH FUSION COMPLICATED BY MASSIVE INFARCTION DUE TO OCCLUSIVE THROMBOSIS OF THE AORTA: CASE REPORT

MARK SAYLOR AND HAROLD GORDON

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Renal ectopia is important chiefly because of certain complications with which it may be associated (Smith and Orkin). It is our purpose to report an unusual and fatal complication of crossed renal ectopia with fusion.

Crossed renal ectopia may occur in several anatomical forms: 1) unilateral fused kidney (with ectopic kidney in the inferior position); 2) sigmoid kidney; 3) lump kidney; 4) "L" kidney; 5) unilateral fused kidney (with ectopic kidney in the superior position); 6) disc or discoid kidney. In the discoid type, the kidney usually lies at the sacral promontory, the pelves face anteriorly and the ureter of the ectopic half crosses the midline to enter the bladder at its normal location. The cause or causes of this anomaly are undetermined, despite the many theories which have been proposed.

The incidence of crossed renal ectopia with fusion was placed by Culp at 1:374, by Abeshouse at 1:1842. Abeshouse could find only 333 cases when he reviewed the literature in 1947. He added 4, bringing the total to 337. Males are affected slightly more frequently than females, the right side of the body more frequently than the left.

Clinical recognition occurs most frequently in the age group 30 to 50 years. A large number of these patients may enjoy a full life span without any significant complaints. The predominating signs and symptoms, if they do occur, consist of a palpable mass, abdominal pain and, less frequently, urinary disturbances (e.g. chills, fever, hematuria, dysuria).

As stated before, the condition becomes significant when a complication ensues. The most frequent complications encountered are infection and hydronephrosis. Other changes noted by Shoemaker and Braasch include calculosis, tuberculosis, actinomycosis, chronic glomerular nephritis, trauma and tumors. Infarction is mentioned but once in the entire series of 337 cases. No details were given in this instance.

Lowsley and Kirwin state that the vascular supply in ectopia is always anomalous. If the kidney lies over the sacrum it may receive branches from the iliac, middle sacral or even the inferior mesenteric arteries. The case reported here presents an unusual combination of an anomalous origin of the renal artery, occlusive thrombosis of the abdominal aorta and massive infarction of the fused ectopic kidney.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

CASE REPORT

H. J. B. (15711) aged 55 years, a white man, was admitted to the Veterans Administration Hospital, Louisville, Kentucky, on March 19, 1948, complaining of "shortness of breath," present about 18 months. His initial symptoms consisted of paroxysmal nocturnal dyspnea, edema of the feet and ankles. Soon thereafter abdominal swelling made its appearance. There was no history of pain in the abdomen. Prior to admission he received mercurial diuretics and digitalis. At first he responded favorably but his symptoms increased gradually and irreversibly.

The past history was noncontributory and systemic review did not disclose any genito-urinary or neuromuscular complaints.

Physical examination revealed an emaciated, dyspneic man whose oral temperature was 94F, pulse 90, respirations 20 and blood pressure 110/70. He had numerous moist rales in both lungs; abdominal distention with a fluid wave; edema of the feet, ankles and presacral region. Palpation of the abdomen revealed no masses and no abnormally palpable viscera.

Initial laboratory findings revealed: normal blood count; urinalysis with specific gravity 1.018, 4 plus albumin, 5–8 white blood cells per high power field, 6–13 finely granular casts per high power field and no red blood cells; nonprotein nitrogen 93 mg. per cent; total protein 4.7 gm. per cent with albumin 2.5 gm. per cent and globulin 2.2 gm. per cent. X-ray examination of the chest revealed signs of bilateral pleural effusion. (Excretory urography was not attempted, due to his critical condition.) An electrocardiogram was interpreted as consistent with myocardial abnormality.

He died 43 hours after admission.

Pertinent findings at the time of autopsy consisted of the following. The kidney was fused and roughly discoid in shape. The upper half extended to the brim of the true pelvis on the right side, the lower half was overlying the pelvic brim, practically in the midline. The renal pelvis of the upper section was well developed and located on the anterolateral surface. The ureter coursed around the organ to enter the right side of the bladder in the normal location. The ureter of the lower portion started from a poorly defined pelvis at the anteromedial border, coursed medially, then posteriorly and entered the bladder on the left side at the usual location. The ureters were small but patent (fig. 1, *A*).

The kidney as a whole was flabby, the lower quarter soft and fluctuant. This region was dark purple in color as were other large areas over the remainder of the organ. On cut section the cortex and medulla were practically indistinguishable (fig. 1, *B*).

The renal artery arose from the right common iliac artery immediately below the bifurcation of the aorta. The upper half of the abdominal aorta revealed many ulcerating intimal plaques. The lower half contained a firm thrombus which was dry, crumbly, firmly attached to the intima and occluded the lumen. This process extended into the renal artery.

The gross pathological diagnoses were: 1) infarct, massive, of fused ectopic kidney; 2) thrombosis with occlusion of the abdominal aorta and renal artery; 3) congenital malformation, crossed renal ectopia with fusion; 4) arteriosclerosis, generalized, severe; 5) cardiac hypertrophy; 6) Laennec's cirrhosis.

Microscopic examination of the tissue sections confirmed the anatomical diagnoses, including renal infarction.

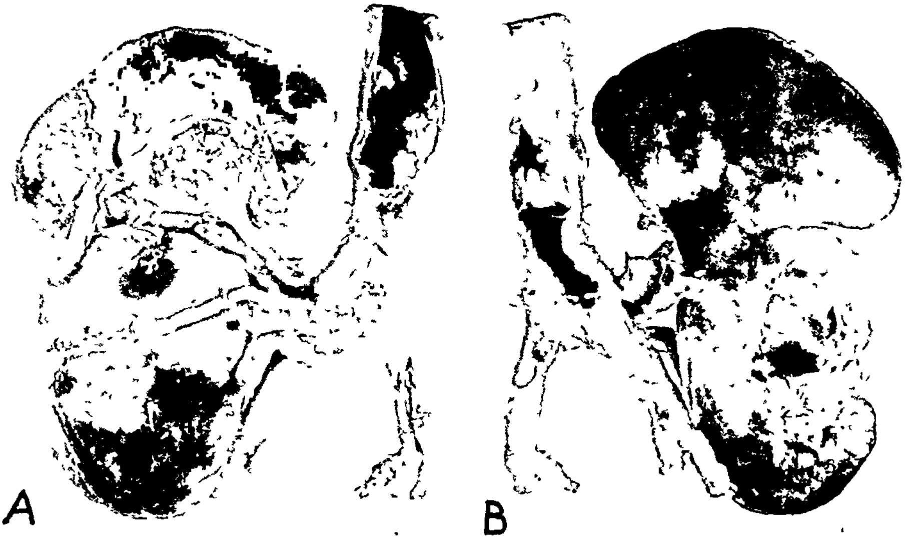

FIG 1 *A*, anterior view of discoid kidney and terminal portion of aorta Kidney is rotated to right in order to afford a better view of blood vessels. Kidney is mottled. Dark areas represent recent infarcts *B*, posterior view of same specimen showing cut surface Note that fusion occurs by means of isthmus.

COMMENT

In this instance neither the renal ectopia nor the aortic thrombosis was diagnosed clinically. Greenfield described acute aortic thrombosis as a relatively infrequent catastrophe which may occur in individuals with chronic vascular disease. According to Straus it may be due to a thrombus superimposed on an embolus which incompletely occludes the aortic bifurcation, or on intimal lesions due to various causes. Infarction of the abdominal viscera and death usually follow.

Slowly progressive occlusive thrombosis of the aorta is even less common. The autopsy incidence has been estimated at 0.12 per cent. Chronic thrombosis is usually a sequel of arteriosclerosis of the aorta. Eddy currents near the aortic bifurcation have been suggested as a contributory factor in the formation of the thrombus. This form has an insidious onset and may have a prolonged course with gangrene of the lower extremities appearing late. It is accompanied by bilateral atrophy of the lower extremities, without evidence of severe trophic changes. Leriche stated that this condition can occur in young adult males His syndrome is characterized by 1) extreme fatiguability in the lower extremities relieved by rest; and 2) inability to maintain an erection. Chronic occlusion is not an immediate threat to life as long as the process occurs below the level of the renal arteries, the viability of the large bowel and lower extremities being maintained by collateral circulation. This case apparently does not fall into the category of chronic occlusion because the clot was recent and unorganized. Since the anomalous vessel of the discoid kidney arose at the aortic bifurcation, the pathogenesis of the massive renal infarction is clear.

SUMMARY

Crossed renal ectopia with fusion is considered briefly.

A case is presented in which the renal anomaly was responsible for the immediate cause of death. This was complicated by aortic thrombosis with occlusion.

The types, incidence and relationship of thrombotic occlusion of the abdominal aorta are discussed.

REFERENCES

Abeshouse, B. S.: Am. J. Surg., **73:** 658–683, 1947.
Culp, O. S.: J. Urol., **52:** 420, 1944.
Greenfield, I.: Ann. Int. Med., **19:** 656–668, 1943.
Leriche, R. and Morel, A.: Ann. Surg., **127:** 193–206, 1948.
Lowsley, O. S. and Kirwin, T. J.: Clinical Urology. Baltimore: Williams & Wilkins, 1944, 2nd edition, pp. 1378–1382.
Shoemaker, R. and Braasch, W. F.: J. Urol., **41:** 1–7, 1939.
Smith, E. C. and Orkin, L. A.: J. Urol., **53:** 11–26, 1945.
Straus, R., Dominguez, R. and Merliss, R.: Am. J. Med. Sc., **211:** 421–427, 1946.

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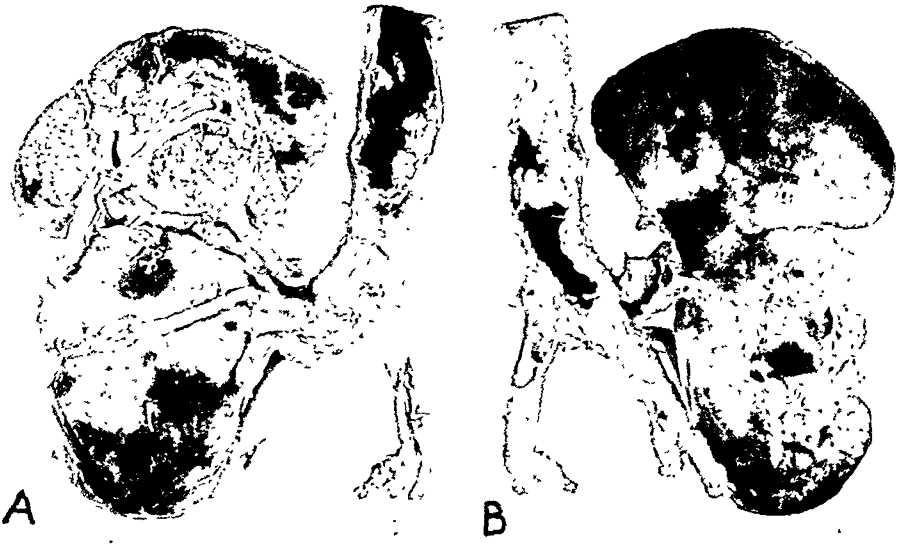

FIG. 1. *A*, anterior view of discoid kidney and terminal portion of aorta. Kidney is rotated to right in order to afford a better view of blood vessels. Kidney is mottled. Dark areas represent recent infarcts. *B*, posterior view of same specimen showing cut surface. Note that fusion occurs by means of isthmus.

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Leriche, R. and Morel, A.: Ann. Surg., 127: 193–206, 1948
Lowsley, O. S. and Kirwin, T. J.: Clinical Urology. Baltimore: Williams & Wilkins, 1944, 2nd edition, pp. 1378–1382
Shoemaker, R. and Braasch, W. F.: J. Urol., 41: 1–7, 1939
Smith, E. C. and Orkin, L. A.: J. Urol., 53: 11–26, 1945
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UNILATERAL POLYCYSTIC KIDNEY IN AN INFANT

R. G. BUNGE AND W. N. HARNESS

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Several reports[1, 2, 3, 4] have appeared in the literature regarding unilateral cystic disease of the kidney. We wish to add one additional case to these.

Throughout our discussion, we shall refer to this as a unilateral polycystic kidney, using the term polycystic to denote multiple discrete cysts of the kidney as opposed to multilocular cysts.

The problem of polycystic disease is often a perplexing one and especially when one is confronted with the unilateral type. Polycystic disease of the kidney in its usual sense, carries a very grave prognosis, and yet if one has a unilateral cystic diseased kidney, one may presume that the prognosis is much better. Recently, we have had a case associated with ureteral aplasia and interesting pathological findings of embryonal cartilage and smooth muscle within the kidney substance.

CASE REPORT

C. D. W., a 5 month old male infant, was admitted to the pediatrics department for examination concerning a defect in the palate, the right eye and an unexplained right upper abdominal mass.

The child had been born at full term following an uneventful pregnancy. A physical examination revealed a white male child of normal height, weight and head size for his age. The right eye presented a micro cornea with a leukoma. The left eye presented a coloboma and a micro cornea. There was also present a bilateral stenosis of the nasolacrimal ducts with secondary infection. Otologically, he had mild catarrhal otitis media bilaterally, hypertrophied adenoids and a congenital defect of the soft palate on the left. The heart and lungs were normal. In the right upper abdomen, a mass could be seen as well as palpated. It was 3 by 5 cm. in diameter, firm, and moved with respiration. The examiner felt that this was kidney. The balance of the examination revealed no congenital abnormalities or defects.

Laboratory studies included urinalysis, negative both chemically and microscopically. The hemoglobin was 12.0 gm. per cubic centimeter. The red blood count was 5,200,000 per cubic centimeter and the white blood cell count was 27,100 per cubic centimeter. The differential blood smear showed 25 per cent segmented polymorphonuclear leukocytes, 70 per cent lymphocytes and 5 per cent monocytes. The fasting blood sugar was 74 mg. per cent. The nonprotein nitrogen was 37 mg. per cent. The blood calcium was 11.7 mg. per cent, and the phosphorus was 6.3 mg. per cent.

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[1] Schwartz, J.: Unilateral multicystic kidney in infant. J. Urol., 35: 259, 1936.

[2] Oppenheimer, G. D. and Narins, L.: Unilateral polycystic kidney diseases. J. Urol., 61: 866, 1949.

[3] Howze, C. P. and Hill, J. H.: Unilateral multiple cysts of the kidney. J. Urol., 61: 187, 1949.

[4] O'Donnell, L. D. and Presti, J. C.: Congenital cystic kidney. J. Urol., 62: 651, 1949.

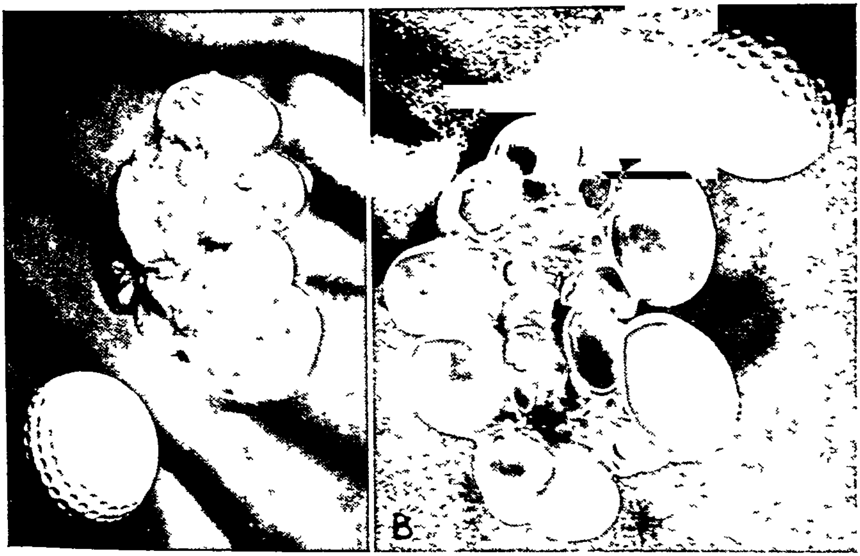

Fig 1 Right kidney *A*, external appearance *B*, cut section showing absence of pelvis and ureter

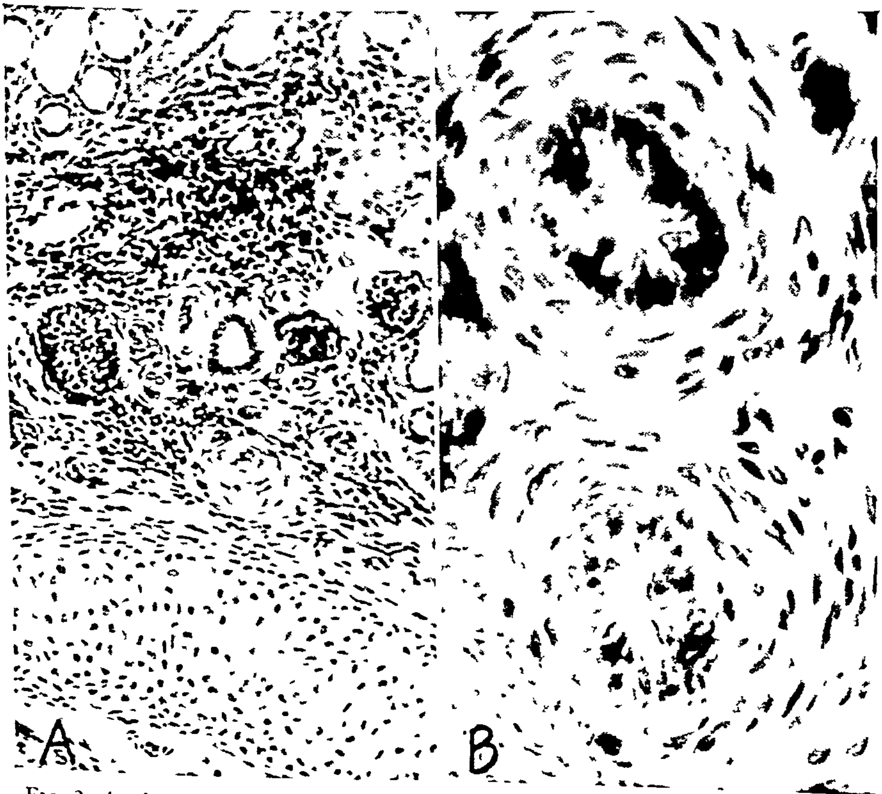

Fig 2 *A* photomicrograph of hilar region showing tubular and glomerular remnants and embryonic cartilage *B* tubular structure surrounded by smooth muscle suggesting coiled ureter.

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CASE REPORT

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The child had been born at full term following an uneventful pregnancy. A physical examination revealed a white male child of normal height, weight and head size for his age. The right eye presented a micro cornea with a leukoma. The left eye presented a coloboma and a micro cornea. There was also present a bilateral stenosis of the nasolacrimal ducts with secondary infection. Otologically, he had mild catarrhal otitis media bilaterally, hypertrophied adenoids and a congenital defect of the soft palate on the left. The heart and lungs were normal. In the right upper abdomen, a mass could be seen as well as palpated. It was 3 by 5 cm. in diameter, firm, and moved with respiration. The examiner felt that this was kidney. The balance of the examination revealed no congenital abnormalities or defects.

Laboratory studies included urinalysis, negative both chemically and microscopically. The hemoglobin was 12.0 gm. per cubic centimeter. The red blood count was 5,200,000 per cubic centimeter and the white blood cell count was 27,100 per cubic centimeter. The differential blood smear showed 25 per cent segmented polymorphonuclear leukocytes, 70 per cent lymphocytes and 5 per cent monocytes. The fasting blood sugar was 74 mg. per cent. The nonprotein nitrogen was 37 mg. per cent. The blood calcium was 11.7 mg. per cent, and the phosphorus was 6.3 mg. per cent.

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[1] Schwartz, J.: Unilateral multicystic kidney in infant. J. Urol., 35: 259, 1936.

[2] Oppenheimer, G. D. and Narins, L.: Unilateral polycystic kidney diseases. J. Urol., 61: 866, 1949.

[3] Howze, C. P. and Hill, J. H.: Unilateral multiple cysts of the kidney. J. Urol., 61: 187, 1949.

[4] O'Donnell, L. D. and Presti, J. C.: Congenital cystic kidney. J. Urol., 62: 651, 1949.

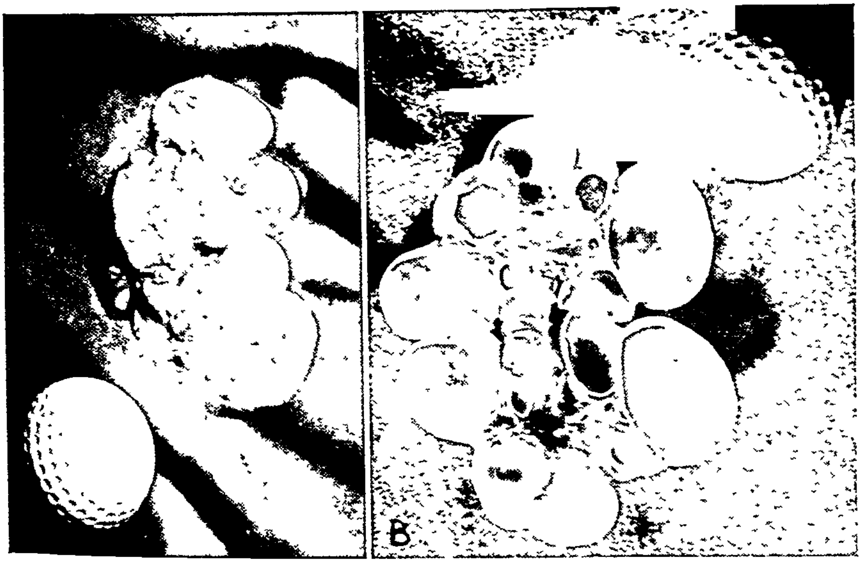

FIG. 1. Right kidney. *A*, external appearance. *B*, cut section showing absence of pelvis and ureter.

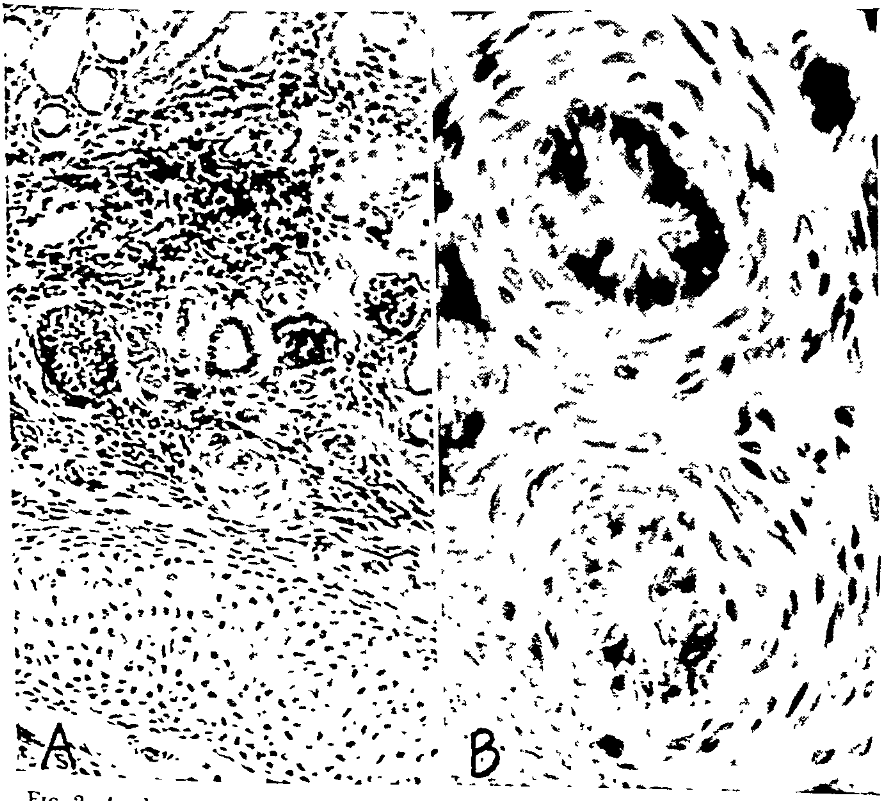

FIG 2 *A*, photomicrograph of hilar region showing tubular and glomerular remnants and embryonic cartilage *B*, tubular structure surrounded by smooth muscle suggesting coiled ureter.

X-ray examinations revealed a healthy chest and repeated excretory urograms showed a normal left kidney and a nonfunctioning right kidney.

Cystoscopy was performed with the baby cystoscope and the bladder was normal. The left ureteral orifice appeared normal and was ejecting clear urine. On the right side of the fully formed trigone was a ureteral dimple but no catheter could be passed into it. No urine was seen issuing from the dimple.

It was believed that the most likely diagnosis was that of a tumor of the right kidney and the patient was referred to the radiological service for therapy. The consultant was of the opinion that there was insufficient proof of malignancy and advised exploration.

Under drop ether anesthesia, the usual curved right lumbar incision was made and on opening Gerota's fascia, a large multicystic mass was encountered in the renal fossa. It had a definite pedicle which was clamped and ligated. No ureter or atrophic thread suggesting a ureter could be found. The mass was easily dissected free from the surrounding tissues and removed.

The gross specimen measured 10 by 8 by 5 cm. and weighed 30 gm. It was composed largely of numerous cystic spaces, some of which were filled with clear straw-colored fluid. The cystic spaces were thin and fibrotic while the walls of the smaller ones were slightly thicker and appeared to contain small amounts of parenchyma. In the hilar region, there was a small amount of fibrotic, noncystic parenchyma. There was no evidence of pelvis or ureter.

Microscopic examinations showed the cyst walls to be composed of hyalinized compact fibrous connective tissue, the inner surfaces of which were lined with a single layer of flattened epithelium. Contained within these walls, were groups of chronic inflammatory cells, a few scattered tubular and glomerular remnants and small ovoid masses of embryonic cartilage. Dissection of the noncystic parenchyma showed extensive scarring, a few scattered atrophic glomeruli and again, several small ovoid masses of cartilage. One large and several small cystic spaces lined by a single layer of cuboidal epithelium, surrounded by a zone of smooth muscle and fibrous tissue were found also. This suggests a kinked and abnormally located ureter.

DISCUSSION

The presence of the renal mass at birth proves its congenital origin. The intact trigone and the ureteral dimple suggest that at one time, the ureteral mucosa was in contact with the bladder, and further, that the tubular elements surrounded with smooth muscle fibers found in the kidney mass, representative of the anatomy of the ureter, suggest a strong possibility that the actual defect in the production of this congenital anomaly lies in the failure of the ureter to fully develop. Since embryologically the ureter develops from below from the wolffian duct, the presence of the ureteral remnants in the kidney substance suggests that it reached this area and then for some unknown embryological reason, failed to completely develop into a normal and functioning ureter. The presence of cartilage raised the question of a teratoma, but none of the elements were found to be invasive. The occurrence of renal cartilage has been reported in hypoplastic kidneys.[5]

Tissue sections were submitted to the Army Institute of Pathology and the consultant believed that the lesion represented a multiple cystic disease of the kidney.

Tissue sections were submitted to Dr. E. T. Bell of the University of Minnesota and he believed it to be a good example of unilateral polycystic disease in an infant. He further expressed the opinion that since the other kidney had normal function, we are safe in assuming that it was not affected.

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[5] Willis, R. A.: Pathology of Tumours. St. Louis: C. V. Mosby Co., 1948, p. 930.

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A number of operations have been devised for the relief of stricture at the ureteropelvic juncture by Foley, Fenger, Dodson and others. However, we believe that the fatty capsule may be utilized with great advantage in all of these surgical procedures, the technique of which will be described below.

The procedure which has given the best results in our hands (fig. 1) consists of exposing the kidney and stripping off the fatty capsule from behind forward in the usual way. After the pelvis has been exposed and the ureter freed, the pelvis is incised just above the stricture and a small probe or groove director is passed through the stricture below into the normal ureter. The stricture is then divided longitudinally through its entire length. A nephrostomy having been done, the ureter is splinted by any method that the operator may prefer. However, our best results have been obtained by using the McIver nephrostomy tube, the tail of the catheter being inserted through the incised stricture for several inches down into the normal ureter.

After this has been accomplished, a part of the fatty capsule is carried underneath the ureter, folded back over the ureter covering the site of the stricture, and sutured to itself. It may also be tacked to the lower pole of the kidney. The kidney is then put back in place and the incision closed. A small Penrose drain is usually advisable.

The outer end of the McIver tube is connected by a rubber tube to a bottle at the bedside. Some antiseptic solution should be injected to keep the tube open. We recommend that the tube be left in place from two to four weeks. After the tubes have been removed there will be very little drainage unless there is some obstruction in lower ureter.

After a week after the tube has been removed, cystoscopy should be done and the ureter gently catheterized, but retrograde pyelography should not be attempted until later.

These strictures should be carefully dilated with a bulb catheter at intervals for quite a while to prevent their recurrence.

CASE REPORT

Mrs. A. reported to our office March 2, 1948. Her chief complaint was pain in the left renal region, nausea, and dizziness. The family history was nonessential. Her past history was unimportant until September 3, 1946. The patient was pregnant, and developed severe pyelitis at about the eighth month. However, she was treated with an indwelling ureteral catheter and was able to go to full term and gave birth to a normal baby boy. She made a rapid recovery and never reported for a urological check up until December 19, 1947. She then complained of a pain in her right kidney. She also was having frequent and painful urination, chills and fever.

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The urine contained blood, pus, etc., and a culture showed the colon bacillus. A mass about the size of a grapefruit could be felt in the right kidney region.

A cystoscopic examination showed an infected bladder. The right catheter met an obstruction at the ureteropelvic junction by which it could not be made to pass. The left side was catheterized without trouble. Plain x-rays were negative for stones. The function on the left side was good, while there was none on the right.

A retrograde pyelogram was attempted with the patient in the Trendelenberg position. No medium could be seen in the right pelvis. but the obstruction was demonstrated very clearly. The left pelvis was essentially normal, but some constriction of the ureter was present at the ureteropelvic juncture (fig. 2, *A*). An excretory urogram confirmed the foregoing findings (fig. 2, *B*).

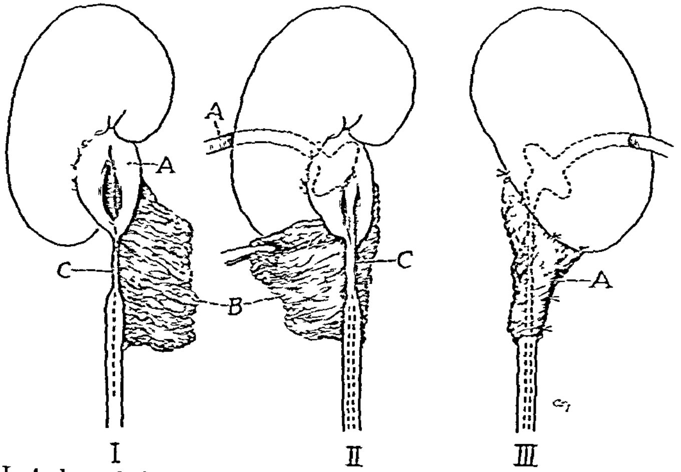

FIG. 1. I. *A* shows kidney has been delivered, pelvis exposed and incised, and smal probe passed from pelvis through stricture. *C*. and down into normal ureter. *B* is part of perirenal fat which is used to cover strictured portion of ureter.

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III. *A* shows stricture which has been covered with perirenal fat.

The patient was hospitalized and after she had been given a transfusion and intravenous injections of glucose, she had so improved that the kidney was removed. The pathologist described the specimen as a very large infected hydronephrosis containing 500 cc of urine and pus. Recovery was uneventful and the patient was dismissed upon the twelfth postoperative day with the instructions to report to the office within 2 weeks for the treatment of the left kidney. She failed to follow instructions and we did not see her again until March 2, 1948, when she was brought to our office complaining of nausea, vomiting, dizziness, scanty urinary output, etc.

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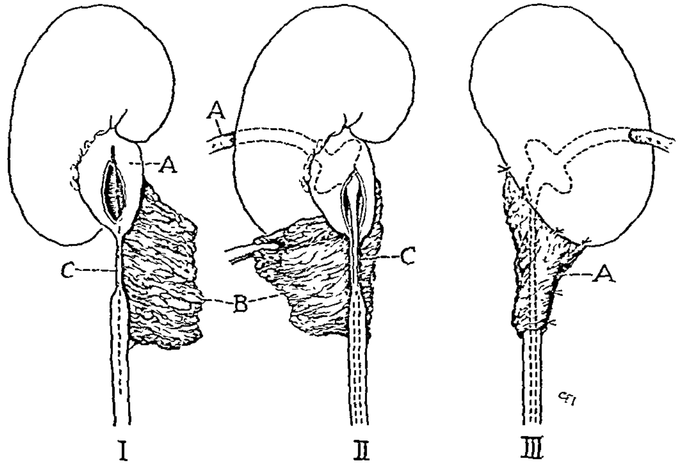

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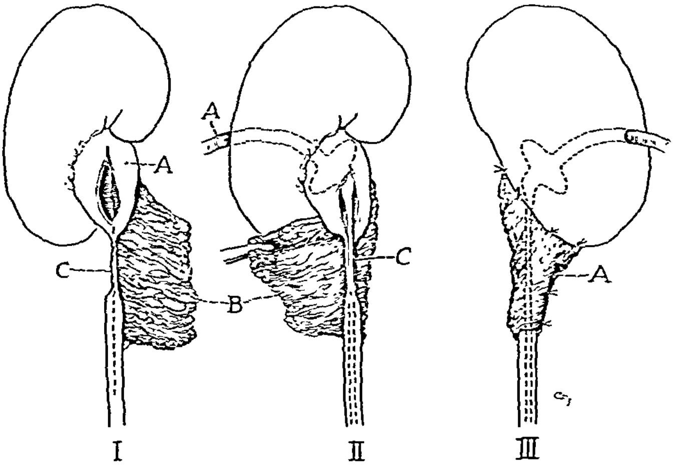

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ture, by which a No. 5 catheter was made to pass with great difficulty. The patient was admitted to the hospital with an indwelling catheter. She improved satisfactorily after the administration of glucose, blood, etc.

We explored the patient's only kidney with fear and trembling. We believed that she could not live unless something was done, but also remembered the very poor results which sometimes followed such surgical procedures. At operation an anomalous vessel was seen crossing the ureteropelvic juncture at which point there was a tight stricture about one inch in length. This was divided longitudinally and a McIver tube inserted according to the technique described above The tube was removed in 3½ weeks. Since then cystoscopy has been done at intervals, dilating the ureter. It is now possible to pass a No. 10 bulb catheter without difficulty and at present the patient's general health is excellent. She does her house work and lives a normal life.

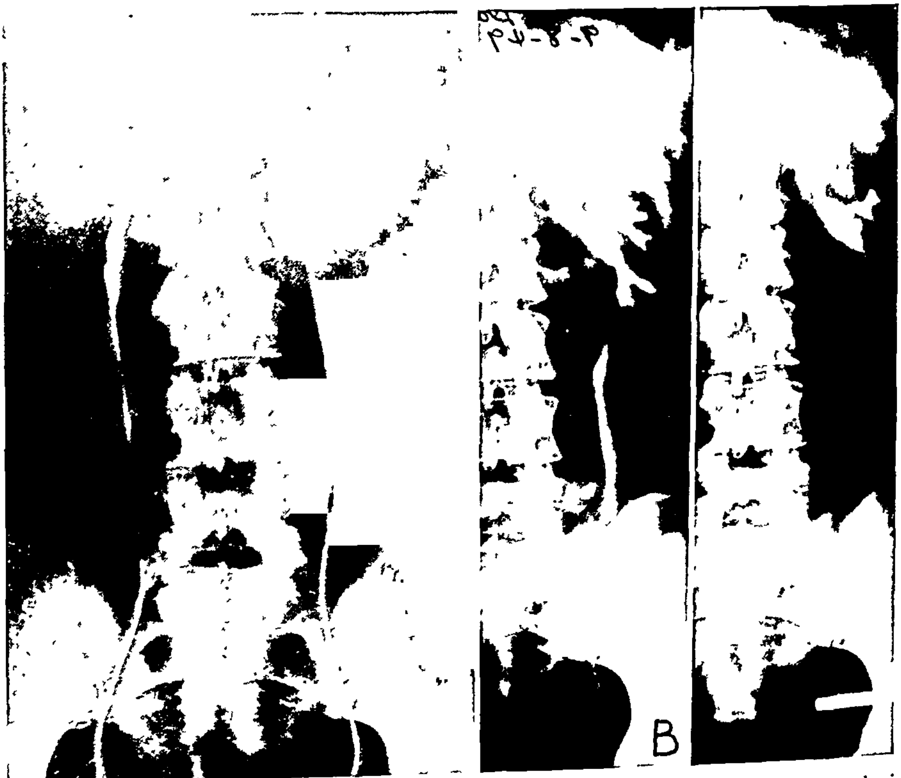

FIG. 2. *A*, pyelogram made prior to removal of right kidney showing complete occlusion of right ureter at ureteropelvic juncture. Also some narrowing of left ureter just below pelvis. *B*, preoperative excretory urogram.

During the past two years we have had occasion to use the technique that we have described in more than ten patients. While some of them have been too recent to evaluate permanent results, their progress has been most satisfactory up to date.

We wish to emphasize the following points: 1) These strictures must be incised and not just dilated at time of operation. 2) The use of the capsule of Gerota, as described, is a great aid in handling these strictures. 3) These ureters must be splinted for from two to four weeks. 4) The McIver tube in our hands has been the best method of splinting. 5) We believe that the use of the capsule of Gerota is one more addition to our armamentarium in dealing with these obstructions at the ureteropelvic juncture.

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THE FOLEY LUMBAR URETEROLITHOTOMY

BRUNO BARELARE

When Foley reported his approach for the removal of calculi from the upper ureter, he gave to the urological surgeon an operative procedure which greatly reduced the morbidity which attends the usual ureterolithotomy. This operation is described as follows: The skin incision extends from a point just below the costovertebral angle and is carried toward the anterior superior spine of the ilium for about eight centimeters. This exposes the triangle of Petit, which is bounded by the posterior margins of the external and internal oblique muscles and the anterior margin of the latissimus dorsi muscle. By means of blunt dissection the margins of these muscles are lifted away from the underlying lumbodorsal fascia. This fascia is incised in the direction of its fibers exposing the perirenal fascia. After stripping this fascia away from the muscles behind it, the ureter is seen immediately under the fascia. The stone can readily be palpated through this fascia and ureterotomy made directly over the stone. The ureter is then closed with fine catgut and the flank closed by approximating the divided edges of the lumbodorsal fascia. No sutures need be placed in the muscles as no muscle fibers have been divided. Foley stated that the postoperative courses were without incident and the patients became ambulant on the second or third day and left the hospital on the fifth to the seventh day. Foley also made a plea against the "conservatism" of prolonged expectancy and manipulation and emphasized the point that such a lumbar ureterolithotomy is far less damaging to the patient, from both a physical and economic standpoint, than a prolonged period of manipulation. The possibility of an eventual pelvic ureterolithotomy, a far more difficult procedure from the standpoint of the patient as well as the surgeon, is always present when manipulative therapy is chosen.

In 1945, Prince called attention to the numerous advantages of the Foley ureterolithotomy and expressed the opinion that the operation has been little used by the great majority of urologists. I agree that this very valuable surgical procedure has not been used as generally as it deserves and wish to make the further point that in my hands, the Foley operation has readily lent itself to other surgical procedures involving the ureteropelvic junction and the renal pelvis, as well as the ureter. In this report some cases are briefly presented to illustrate the use of this exposure in the surgical treatment of various ureterorenal lesions.

CASE REPORTS

Case 1. J. K., St. V. No. M-8194, a 25-year-old white married woman, first began having pain in the right flank about 4 months before examination. At that time she was in her last month of pregnancy. She had had considerable fever with pus in the urine. She recovered from this and went on to term without difficulty. One month before examination she had had an attack of pain in the left flank. An x-ray of the abdomen made at that time showed a calcific shadow

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in the region of each kidney. Cystoscopy was carried out and pyelograms were made. Both renal pelves were bifid but were otherwise normal. Preliminary studies and laboratory examinations were adequate. Urinalysis showed 1–6 white blood cells per high powered field, and an occasional red cell. On January 20, 1947, the left flank was opened under spinal anesthesia through a Foley exposure, the ureter easily identified and traced up to the kidney pelvis. A small incision was made in the pelvis and the stone easily extracted with stone forceps. The defect in the pelvis was closed with two interrupted sutures of 0000 chromic catgut. A small rubber drain was left down to this area and the lumbodorsal fascia closed with several interrupted sutures of No. 1 catgut. On the third postoperative day the patient was ambulant and there was only slight urinary drainage from the flank. On the ninth postoperative day she left the hospital with the incision well healed and the patient comfortable. The highest temperature during her hospital stay was a spike of fever up to 100.4F on the first postoperative night.

She returned to the hospital in August 1947, and had the same procedure done on the right side. Her convalescence was again very smooth and her highest temperature was 100F on the second postoperative day. She was allowed up on the second postoperative day and walked about on the fifth postoperative day. She was discharged on the sixth postoperative day. There was no urinary drainage after the second day postoperatively.

Case 2. R. E., St. V. No. X-2385, a 23-year-old white man, first had pain in both flanks in September 1946. About one year later, he had another attack of pain and at that time an x-ray revealed stones in both kidneys. Cystoscopic studies were carried out and an excretory urogram made. Both kidneys functioned well and were seen to be normal in structure. Two moderate sized stones were in the right kidney and on the left side, one moderate sized stone and one very small linear shadow. On October 23, 1947, the left flank was opened through a Foley incision and the upper ureter identified. The pelvis was exposed and the stone could be easily felt within the lumen of the kidney pelvis. The pelvis was opened and the larger calculus removed. The calyces were probed very carefully in search of any other possible stone, but none was found. A catheter was then passed into the kidney pelvis and the pelvis irrigated with normal saline. The pyelotomy opening was closed with one suture of 0000 chromic catgut and a drain left down to this area. The lumbodorsal fascia was closed with interrupted chromic No. 1 and the skin closed with interrupted black silk. On the first postoperative day the patient's temperature spiked to 101.4F, but thereafter fell to normal. Some nausea occurred for three days postoperatively. For this reason, the patient was not allowed up until his fourth postoperative day. He walked on the next day and was discharged healed on the ninth postoperative day.

He returned to the hospital in December 1947 to have the right kidney operated on. The Foley incision was made and the pelvis of the kidney exposed. Both stones were removed easily, although the second stone was very soft and broke up when grasped with the stone forceps. It was removed piecemeal and the pelvis irrigated throughly through a catheter. One small 0000 catgut suture served to close the opening in the pelvis and a drain was left down to this point.

The lumbodorsal fascia was closed with interrupted sutures of chromic No. 1 catgut. The highest postoperative temperature was 100.6F on the third postoperative day but dropped to normal soon thereafter. There was little urinary drainage from the flank. The patient had a good bit of pain in the area of incision and did not want to get out of bed until the fifth postoperative day. He was discharged on the ninth postoperative day.

It might be added that this patient has felt very well postoperatively and has regained 30 pounds. However, a recent x-ray reveals a shadow in the left kidney about 1 cm. in diameter. This may have been due to the fact that a minute stone was left behind at the first operation or may be due to this patient's stone forming tendency. This however, does not detract in any way from the value of this exposure.

Case 3. C. S., St. V. No. N-3051, a 33-year-old white married woman, had been having intermittent attacks of pain in the left lumbar region over the preceding year. Three weeks previously she had had a very severe attack requiring opiates. She had been comfortable since. Except for some tenderness in the left flank, the physical examination was not abnormal. Urinalysis revealed the presence of 2–8 pus cells per high powered field with occasional clump. The urine was alkaline. Cystoscopy and x-ray studies showed a shadow just to the left of the third lumbar vertebra which measured 12.0 by 7.0 mm. On December 6 the calculus was removed through a Foley exposure and a single suture of 00000 catgut was used to close the ureterotomy. The patient was allowed up in a chair on the third day and walked about on the fourth day. On the seventh day she was discharged from the hospital healed and afebrile. Her highest temperature elevation during the postoperative period was 100.6F. The minimum amount of discomfort postoperatively is evidenced by the fact that she received only one hypodermic of pantapon, gr. 1/3 during her convalescence.

Case 4. E. O., St. V. No. N-4303, a 54-year-old white married woman, had had a sudden attack of severe pain in the left lumbar region radiating around to the lower abdomen 6 weeks before she was first seen. With the help of some opiates the pain had disappeared but had recurred the night before the patient was first seen. There had been no hematuria and there had been no lower urinary tract symptoms. There had been chills and fever with both attacks. X-ray studies revealed a calculus in the left ureteropelvic area. On March 2, 1948, through a Foley exposure, the ureter and renal pelvis were identified. The stone was palpated in the region of the ureteropelvic junction. An incision was made in this area and in attempting to extract the stone it slipped back into the renal pelvis and was located with a stone forceps in the upper calyx. It was then removed. The closure was as previously described after the patency of the ureter was confirmed by passing a catheter down the ureter into the bladder. She drained very little urine postoperatively and was allowed out of bed on the third postoperative day, and discharged healed on the eighth postoperative day. This patient had a spike of fever up to 103F on the first postoperative night but dropped to normal over the next 48 hours.

Case 5. J. M., St. V. No. N-4501, a 67-year-old white woman, was referred because of intermittent frequency of urination over the past year. She had been found to have pus in the urine on several occasions. On examination the urine was found to be cloudy and contained a great many pus cells and numerous red blood cells. Complete studies were made and an x-ray revealed a large stone in the pelvis of the right kidney. On March 26, 1948, this stone was removed through a Foley incision and the usual closure with drainage was made. This patient had fever up to 102F on the first and second postoperative nights, but it fell to normal during the third postoperative day. She was allowed out of bed on the third postoperative day. She was allowed to stay in the hospital until the thirteenth postoperative day because she lived by herself and had no one to take care of her at home.

Case 6. Mr. C. B., St. V. No. X-5884, a 61-year-old white schoolteacher, complained of fever and left flank pain for the preceding 2 years. There had also been a history of painful swelling of various large and small joints. At the time of examination, the right knee was swollen and tender and had been for several weeks. There was some enlargement of the heart with a blood pressure of 154/82. The medical consultant made a diagnosis of hypertensive heart disease and rheumatoid arthritis. The urine contained a rare pus cell and was acid in reaction. Urological studies revealed the presence of a calculus filling the left kidney pelvis. The calyces on this side were quite normal, however, and there was no dilatation around the stone in the pelvis of the left kidney. The right urinary system was completely normal. At operation, June 16, 1948, the left renal calculus was removed through a Foley exposure. The patient tolerated the procedure very well and had profuse urinary drainage for the first 5 days after operation. There was no recurrence of the urinary drainage after the sixth postoperative day. On the eleventh postoperative day he was found to have a wound infection and 3 ounces of pus were evacuated. The incision then rapidly healed. He was discharged 15 days after operation. The patient was not allowed out of bed until his ninth postoperative day in view of the arthritis in the right knee. His temperature on the second postoperative day was 99.8F and then dropped to normal until the wound infection appeared, at which time it went up to 102.2F. After the pus was evacuated it dropped to normal within 2 days.

Case 7. Mrs. P. F., St. V. No. X-6034, a 50-year-old white woman had suffered for many years with pain in the right side. She was told in 1940 that she had a stricture of the right ureter. The ureter was apparently dilated in 1941 and again in 1945. In the 18 months preceding admission she had complained of burning and frequency, with some pain in the right flank which was markedly accentuated when she was up and about. The physical examination revealed no abnormality except for the fact that the slightly tender lower pole of the right kidney was easily palpable. The urine contained 1–4 pus cells and a rare red blood cell. X-ray studies revealed hydronephrosis of the right kidney due to a deformity at the ureteropelvic junction. On June 25, 1948, the Foley exposure was carried out on the right side and the ureter identified. The kidney was found to be quite movable and consequently all of the kidney except for a small area in the region of the upper pole could be mobilized without difficulty. In view of the fact that a nephropexy was also to be done, it was decided to extend the incision posteriorly by dividing one inch of the latissimus dorsi muscle. This gave very adequate exposure. The classical Foley Y-V plastic was performed and a 12F rubber catheter was placed down the ureter through the site of repair and brought to the outside through the lower pole of the kidney. A nephropexy was then carried out by splitting the capsule of the kidney on the convex surface and suturing the capsule with chromic catgut as high as possible in the right retroperitoneal gutter. A drain was left down to this area and the flank closed in the usual fashion. Two chromic No. 1 sutures were placed in the small incision through the latissimus dorsi muscle. On the fourth postoperative day the drain was started out. The catheter was irrigated daily. The sutures were removed on the sixth postoperative day and on the following day the drain was removed. On the eleventh postoperative day the rubber splinting catheter was removed as it would not irrigate. Following the removal of this catheter, there was no urinary drainage from the flank. She was allowed out of bed on the seventeenth postoperative day and was discharged on the twentieth postoperative day, healed, comfortable and afebrile. The patient, of course, was kept in bed for a prolonged period of time because of the nephropexy and also the presence of the splinting catheter. The Foley exposure was used here purely as a test to see if adequate exposure could be obtained.

Case 8. Mrs. E. B., J. H. No. 73036, a 45-year-old white woman, complained of pain in the right side for 4 to 5 years. Her last attack of pain 6 weeks before admission was very severe and also accompanied by hematuria, frequency and urgency. On examination the temperature was 99F. There was tenderness in the right lower quadrant and in the right lumbar region. The urine contained an occasional pus cell and was acid in reaction. Culture of the urine resulted in the growth of a B. hemolytic streptococcus. A flat film of the abdomen revealed a density of 1 cm. in diameter, apparently in the region of the right ureter. There was also seen a minute shadow overlying the soft tissue shadow of the right kidney and also one in the renal region on the left side. Cystoscopy was carried out and a catheter passed up the right side with some difficulty, as there was apparently a small calculus just above the right ureterovesical orifice. The calculus was seen to occupy a position in the upper third of the right ureter just at the ureteropelvic junction. The right pelvis could not be visualized due to the calculus. The catheter on the right side was left indwelling in an attempt to dilate the right ureter to facilitate the passage of the small stone in the lower ureter. The next day the indwelling catheter was removed and 2 days later a follow-up x-ray revealed that the small stone in the right lower ureter had been passed. Excretory urography disclosed a double ureter and double pelvis on the left side. Some of the dye appeared in the upper portion of the right kidney, but none was seen in the lower portion. It was apparent that a similar reduplication existed on the right side.

On August 11, 1948, a Foley ureterolithotomy was done on the right side. The ureter was easily identified and the calculus removed. A Penrose drain was inserted down to the ureterotomy and the flank closed by interrupted sutures of chromic catgut through the lumbodorsal fascia, and approximation of the muscles with plain catgut. The drain was removed on the fourth postoperative day. The patient was allowed out of bed on the second postoperative day. She was discharged on the sixth postoperative day. Her highest postoperative temperature was 100F on the day following operation and rapidly fell to normal.

Five weeks later the patient returned because of pain in the left side with chills, fever and burning on urination. X-ray revealed the small density previously described in the left kidney area, but the other previously reported densities were no longer present. Excretory urography showed good filling on both sides and there was no evidence of dilatation of the ureters, pelves or calyces. A chest film was normal. The patient was given penicillin and was comfortable within 24 hours. She was discharged at the end of a week. She was given an acidifier and an acid ash diet. She has remained free of symptoms up until the present time and is being followed in the clinic. There has been no change in the size of the small stone in the left kidney.

Case 9. L. R., J. H. H. No. 91259, a 57-year-old Negress, complained of pain in the right abdomen and back for the preceding 8 years. Three weeks before admission she had an attack of burning on urination with increasingly severe right abdominal and back pain. There had also been some fever, but no chills. The pain became so severe that she was unable to stand erect. In the right side of the abdomen could be felt a hard, nodular mass which was movable. This mass was approximately 5 by 10 cm. in size. The urine contained innumerable red blood cells and 3–8 white blood cells per high powered field. The pH was 8.0. Cystoscopy was performed. Retrograde pyelograms showed, on the right side, a low kidney with a widely dilated kidney pelvis and an obvious obstruction at the ureteropelvic junction. In this area there could be seen a large staghorn calculus. The left kidney was within normal limits.

On December 20, 1948, a right nephrectomy was performed through a Foley incision. The ureter was divided and ligated following which a large aberrant vessel coursing across the ureteropelvic junction was divided. The pedicle was identified and dissected free of the surrounding fat. Pedicle clamps were placed and the kidney removed. The pedicle was secured with No. 1 chromic transfixion suture. The lumbar dosal fascia was closed with interrupted chromic catgut, following which the separated muscles were approximated. Two drains were left down to the renal fossa. She tolerated the procedure very well and was returned to her room in satisfactory condition. Her highest postoperative temperature was 100F. There was very little drainage from the wound, and the drain was removed on the fourth postoperative day. She was allowed out of bed on the same day and was discharged on the seventh postoperative day.

Case 10. F. O. S., St. V. No. N-8899, a 29-year-old white woman, came in with a complaint of weakness over the preceding 6 months. She had noted cloudy urine, and 6 weeks before admission had suffered an attack of severe right flank and abdominal pain, which was accompanied by nausea and no vomiting. On examination, the right kidney was palpable and somewhat tender. The urine contained 6–8 pus cells with an occasional red blood cell. Cystoscopy was carried out and x-ray studies made. Multiple calculi were seen in the right renal pelvis. On January 6, 1949, the right kidney was exposed through a Foley excision and the ureter was identified. This was traced up to the kidney pelvis which was incised and the two larger stones, plus one very small stone, were removed. The pyelotomy was closed with interrupted suture of 0000 chromic catgut. The flank was closed in the usual method and a Penrose drain left in place.

The patient tolerated the procedure well and was returned to her room in satisfactory condition. She had considerable discomfort for the first 3 days after operation and had some difficulty in voiding. She had to be catheterized on four different occasions. On the fourth postoperative day she was allowed up in a chair and on the following day the drainage through the flank had ceased. The sutures were removed on the sixth postoperative day and she was discharged on the tenth postoperative day.

Case 11. H. G., St. V. No. N-9823, a 31-year-old white woman, had known that she had a kidney stone for several years and had had several episodes of pain in the right lumbar region. There was also a history of chills, fever and incessant vomiting. At the time she was seen in the office, she had had pain for the past 5 days with severe pain over the previous 24 hours. The temperature, pulse and respirations were normal. There was severe tenderness in the right lumbar region but no mass. Except for obesity, the remainder of the examination was normal. Urine contained an occasional pus cell. Cystoscopy was carried out and an obstruction was met in the middle third of the right ureter. The x-ray confirmed the presence of a stone in this region. An emergency Foley ureterolithotomy was carried out in the usual manner on March 10, 1949. After the stone was removed, a ureteral catheter was passed down to the bladder and also up into the kidney pelvis to be sure that no other obstruction remained. The patient did not sit up the day after operation because she was still somewhat nauseated, but on the next day she sat up in bed and on the following day was allowed out of bed. At this time there was no more urinary drainage from the flank. She was discharged healed, afebrile and comfortable seven days after operation. The highest temperature postoperatively was 100F 24 hours after operation.

Case 12. I. G., St. V. No. O-1121, a 43-year-old white woman, was admitted with a complaint of pain in the left lumbar region and left abdomen with nausea and vomiting for 2 weeks. There had been considerable abdominal distention. On examination, the abdomen was moderately distended with tenderness over the left abdomen and flank. The urine contained many red blood cells and no pus cells. X-ray studies revealed a nonfunctioning left kidney with a stone shadow in the region of the left ureteropelvic junction. On June 10, 1949, the Foley exposure was made on the left side and the ureter identified. It was traced up to the kidney pelvis and calculus was easily palpable at the ureteropelvic junction. The ureter was opened just below the stone and it was attempted to grasp the stone with forceps, but the calculus dropped back into the lower calyx of the kidney. It was removed with forceps after some manipulation. The ureter was closed and a drain left down to this site. The flank was closed with chromic

No. 1 catgut. The patient tolerated the procedure well and was returned to her room in satisfactory condition. She drained profusely for the first few days and gradually stopped draining by the seventh postoperative day. She was allowed up on the fourth postoperative day, and discharged on the eleventh postoperative day.

Case 13. A. O., J. H. H. No. A-6550, a 35-year-old white man, complained of severe pain in the left lower quadrant and in the right flank, for over the preceding 7 weeks. He stated that these symptoms had been present in much milder form for the past 7 to 8 years. There had been some hematuria from time to time with occasional bouts of dysuria. For a number of months the urine had been cloudy, but there had been no chills or fever. Four to five weeks before, he had been operated on for a perforated peptic ulcer. On physical examination, the temperature was 99.4F. The urine contained a rare red blood cell, 7–10 white blood cells and was acid. Culture of the urine resulted in the growth of a hemolytic staphylococcus and streptococcus. A flat x-ray revealed a rounded calculus in the left renal area about 1 cm. in diameter. In the lower portion of the right renal area a slight small triangular stone was seen. Retrograde pyelograms were within normal limits, except for a slight dilatation of the left kidney pelvis.

Operation was carried out on September 19, 1949 and through a left Foley incision the renal pelvis was identified and incised. The stone was removed without difficulty and the pelvis closed with one small chromic suture. A drain was left down to this area and the flank closed in the usual fashion. He tolerated the procedure very well. On the following day he was allowed to sit up in bed and was allowed out of bed on the second postoperative day. His highest postoperative temperature was 99.8F on the day following operation and rapidly fell to normal. He was discharged on the seventh postoperative day, healed, comfortable and afebrile.

He returned for a right kidney operation and this operation was carried out on October 25, 1949. Some difficulty was encountered in grasping the stone which lay in the inferior calyx and finally a small stab wound was made through the kidney substance into the calyx. The stone was then easily removed. One mattress suture was used to close the nephrotomy and one suture of fine catgut was used to close the renal pelvis. A drain was left in place and the fascia closed as usual. The highest postoperative temperature was 99.4F on the first postoperative day and thereafter it fell to normal. He was up in a wheelchair on the fourth postoperative day, and on the next day walked about. The drainage ceased on the ninth postoperative day and the patient was discharged on the eleventh postoperative day.

It should be stated that should the operator decide that he does not have adequate exposure, due to adhesions, congenital abnormalities, or any other cause, he can easily enlarge this exposure for the classical muscle-cutting one. The division of the latissimus dorsi muscle alone frequently suffices. If necessary, the oblique musculature can be divided also. Thus the operator has not placed himself in a position where he has irrevocably limited himself to an exposure that might not prove suitable

SUMMARY

Thirteen cases are presented in which various urosurgical procedures were carried out through the Foley lumbar exposure.

It is emphasized that this exposure can be used successfully in pyelotomies, pyelolithotomies, ureteropelvic plastic procedures and nephrectomies.

This muscle-splitting incision allows shorter operating time, earlier ambulation and a shorter and more comfortable convalescence.

In the event that the exposure is not adequate in the case at hand, no time has been wasted as the incision can readily be extended and the classical exposure obtained

REFERENCES

Foley, F. E. B.: Management of ureteral stone. Operation versus expectancy and manipulation. J. A. M. A., **104**: 1314–1318, 1935.

Prince, C. L.: Lumbar ureterolithotomy. Foley operation. J. Urol., **54**: 368–373, 1945.

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CONGENITAL URETERAL DILATATION WITH RENAL HYPERPARATHYROIDISM

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Despite intensive investigation,[1–12] the etiology of congenital ureteral dilatation remains obscure. The lack of information regarding the neuro-anatomy and neurophysiology of the ureter is a major cause for the confusion. Lapides[4] conducted an extensive series of experiments and believes that neither the sympathetic nor parasympathetic nervous systems have any effect on the ureter, and concludes that the ureter is an autonomous organ not affected by the central nervous system.

Summerfeldt and Brown[5] reported a case in 1934 of persistent pyuria accompanied by dilated ureter in a 13 month old infant which they believed was due to neurogenic dysfunction of the ureter. A presacral sympathectomy was performed, and post-mortem findings on this patient were reported 15 years later when death occurred.[6] These investigators and others[7] have since concluded that sympathectomy is valueless. Should the work of Lapides be confirmed, the reason for the failure of that type of surgery will be readily understandable.

Vermooten[9] believes that the great majority of congenitally dilated ureters in children is due to a persistent Chwalla's[1] membrane just at or above the ureterovesical junction. He believes that the continued pressure of urine on this membrane causes sufficient ischemia to the ureter to result in fibrosis and stricture at the ureterovesical junction.

The nomenclature pertaining to ureteral dilatation is also unsettled, largely because of the varied theories for etiology. This is particularly true as regards the differentiation between megalo-ureter and hydro-ureter, but the most prevalent general opinion is that megalo-ureter applies to a nonobstructive ureteral dilatation, while hydro-ureter is the result of obstruction.[8] Whatever the specific cause of ureteral dilatation, in the absence of more conclusive information, the question of etiology of this abnormality must remain obscure, and etiological theories may be considered in three groups: 1) obstruction, 2) congenital malformation, and 3) neurogenic dysfunction.

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[1] Chwalla, R.: The process of formation of cystic dilations of the vesical end of the ureter and of diverticula at the ureteral ostium. Urol. & Cutan. Rev., **31:** 499, 1927.

[2] Vermooten, V.: The elongation of the ureter. J. Urol., **23:** 427, 1930.

[3] Vermooten, V.: A new etiology for certain types of the dilated ureters in children. J. Urol., **41:** 455, 1939.

[4] Lapides, J.: The pathology of the intact human ureter. J. Urol., **59:** 501, 1948.

[5] Summerfeldt, P. and Brown, A.: Chronic pyuria-presacral sympathectomy. J. Pediat., **5:** 735, 1934.

[6] Lehman, E. and Hardyment, A. F.: Chronic pyuria-presacral sympathectomy (final report). J. Pediat., **34:** 640, 1949.

[7] Wayman, T. B.: Surgery of megalo-ureter. J. Urol., **61:** 883, 1949.

[8] Campbell, E. W.: Megalo-ureter. J. Urol., **60:** 31, 1948.

[9] Vermooten, V.: Personal communication, 1949.

[10] Lucas, R. C.: On a form of late rickets associated with albuminuria, rickets of adolescents. Lancet, **1:** 993, 1883.

[11] Von Recklinghausen, F.: Die Fibrose oder deformirende Ostitis, die Osteomalacie, und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen. Separatabdruck aus der Rud. Virchow zum 13 October 1891 gewidmeten Festschrift der Assistenten, Berlin, 1891.

[12] Park, E. A. and Eliot, M. M.: Brennemann's Practice of Pediatrics III, chapter 29.

It is the purpose of this paper to report a case of hyperparathyroidism and associated skeletal lesions secondary to renal insufficiency arising from bilateral ureteral dilatation. This case is noteworthy in that it demonstrates the insidious onset and slow progression of the disease, as well as the remarkable compensatory reaction of the body to slowly developing but severe derangements of the blood chemistry.

CASE REPORT

C. C. H. No. 11777. A 14 year old white boy entered the hospital with the chief complaint of progressively increasing polydipsia, polyuria, and persistent albuminuria of approximately 8 years' duration. From birth the child had had frequent attacks of severe upper respiratory infection, but he had no history of scarlet fever, specific renal infection or symptoms referable to the genito-urinary system. The past and family history was not otherwise revealing.

Physical examination revealed a pale, poorly developed child who weighed 69 pounds, and appeared about 10 years of age. His face was puffy and mild peri-orbital edema was present. No other abnormality of the head, neck, heart or lungs were found. Palpation of the abdomen revealed a mass in the left upper quadrant of the abdomen. The blood pressure was 110/65. There were no other positive physical findings.

The urine was acid, specific gravity 1.014, sugar negative, albumin 2 plus; microscopic examination revealed 2–4 leukocytes per high power field, and an occasional erythrocyte. No casts were found. Urine culture revealed no growth. At no time during the hospital stay was the patient able to concentrate urine above 1.015, even on rigid fluid restriction.

Hemoglobin determinations averaged 59 per cent (14.7 gm. equal 100 per cent), with 3.0 million erythrocytes, 11,400 leukocytes, and a normal differential. The sedimentation rate averaged 55 mm. (Wintrobe).

Blood serum protein level was 8.1 gm., with albumin equal to 5.5 gm. and globulin 2.6 gm. The nonprotein nitrogen averaged 191 mg. per cent with a maximum of 243 mg. per cent and a minimum of 122 mg. per cent. The CO_2 combining power was 15 mg. per cent, serum chlorides 617 mg. per cent, serum calcium 11.0 mg. per cent, serum phosphorus 6.25 mg. per cent. Alkaline phosphatase was 10.8 Bodansky units. Blood creatinine was equal to 8.0 mg. per cent. Total blood cholesterol was 461 mg. per cent.

Despite these grossly distorted blood chemistry values, the patient was in no apparent distress, complaining only of intermittent weakness. When the acidosis was corrected, and the CO_2 combining power raised to 45 volumes per cent, the serum calcium fell to 6.4 mg. per cent, despite the administration of calcium chloride.

Tetany was observed on only one occasion during the hospital stay, and was treated by intravenous injection of 10 per cent calcium gluconate.

The kidneys were indistinctly outlined on a flat film, but appeared to be enlarged. An excretory urogram revealed no dye in the kidneys, ureters, or bladder. Retrograde pyelography was then performed. A cystoscope passed easily into the bladder, which was found to be completely free of abnormality. The mucosa was pink-white, there was no exaggeration of the blood vessels and no evidence of tumor, calculus, or infection. The bladder wall showed no evidence of trabeculation.

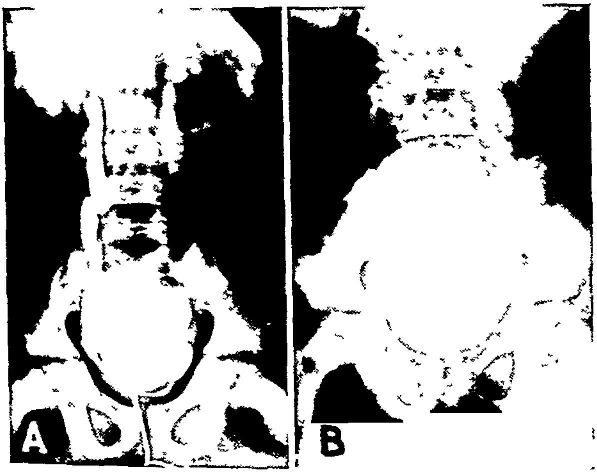

Fig. 1. *A*, bilateral pyelogram revealing tremendous dilatation and tortuosity of both ureters. Note irregularity of epiphyses *B*, cystogram of dilated bladder.

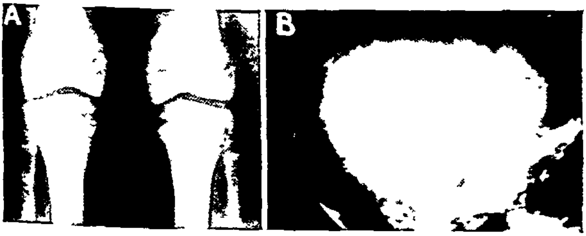

Fig. 2. *A*, showing grossly irregular, widened epiphyses of femurs and tibiae *B*, showing large cystic area in skull

The urethra was observed, and there was no evidence of any obstructive process in the nature of congenital valves. The ureteral orifices were in normal position, slit-like, refluxing normally, and free of obstruction or narrowing. No. 4 ureteral catheters were easily passed a distance of 20 cm. on both sides and there was no evidence of ureteral obstruction. The ureteral drip was steady, rapid and productive of clear, water-like urine. Phenolsulfonphthalein was injected intravenously; no excretion of the dye occurred 1 hour later. Bilateral pyelography revealed enormous dilatation, tortuosity, and kinking of both ureters (fig. 1, *A*). No narrowing of either ureter was seen. Both ureters filled well, but no dye entered the kidney pelves or calyces. The bladder appeared to be greatly dilated on x-ray examination (fig. 1, *B*). Cultures of urine from both kidneys and ureters, and from the bladder were negative.

X-ray films of the long bones revealed gross irregularity of the epiphyses of the femurs, the humerus, and in the lower end of the tibia, with widening of the epiphyseal lines. There was a diffuse osteoporosis of all the shafts (fig. 2, *A*).

Lateral films of the skull revealed many irregular, rounded, cystic areas, none larger than 1 cm. in size (fig. 2, *B*). The pituitary fossa was normal in size, outline, and position.

This patient is being observed at regular intervals in the outpatient clinic. The patient's symptoms have persisted but are not greatly increased in severity. The derangement of the blood chemistry findings has, however, become more marked. During the most recent outpatient visit, these values were as follows: the blood serum calcium was 12.2 mg. per cent, the alkaline phosphatase 56.3 Bodansky units, with a nonprotein nitrogen of 134 mg. per cent and a CO_2 combining power of 30.

DISCUSSION

Despite the fact that many aspects of this syndrome, in particular those relating to the metabolism of calcium, are not clear, most investigators agree that the primary lesion is renal, and that the skeletal changes are a consequence of the secondary involvement of the parathyroid glands. The renal lesions may vary widely; most commonly the kidneys present a combination of defective development and infection. Among reported renal lesions are congenital urethral valves at the vesical outlet, cystic kidneys, solitary atrophic kidneys, chronic nephritis, and obstructive uropathy. The ultimate consequence of any of these lesions may be renal insufficiency. The presence of extreme renal insufficiency of long duration is all that is necessary for development of this syndrome.

One of the early consequences of renal insufficiency is increased retention of nitrogenous products, which is almost always accompanied by parallel retention of phosphorus due to inability of the kidney to excrete endogenous waste phosphates. Mitchell[13] believes that the retained phosphorus is readily capable of precipitating calcium in the intestinal tract as the insoluble calcium phosphate, which is excreted by the bowel. The result is failure of calcium absorption, and calcium starvation occurs.

The exact sequence of events by which renal insufficiency results in increased parathyroid activity is not clear, but Albright and his co-workers[14] have suggested that low blood calcium provides the stimulus for hypertrophy of the parathyroid

[13] Mitchell, A. G.: Nephrosclerosis in childhood. Am. J. Dis. Child., 40: 101, 315, 1930.

[14] Albright, F., Drake, T. G., and Sulkowitch, H. W.: Renal osteitis fibrosa cystica. Bull. Johns Hopkins Hosp., 60: 377, 1937.

glands, and Pappenheimer[15] states that the parathyroid glands react to the loss of renal tissue by an increase in volume which is roughly proportional to the severity of the renal disease.

Whatever the immediate stimulus to parathyroid hypertrophy, the excessive secretion of parathyroid hormone results finally in increased osteoclastic activity and the skeletal lesions described as osteitis fibrosa cystica. There may be wide variation in the character of the skeletal lesions,[12] and osteoporosis, delay and irregularity in ossification, epiphyseal irregularity and separation, and bony translucency have all been described. Albright et al.[16] state that skeletal involvement is an index of the duration and not the severity of the disease, and believes that the age of onset of the disease is the final determinant of the type of bony lesion which occurs; thus, the younger the age of onset, the greater will be the damage to the epiphyses.

The case reported here is marked by regular elevation of serum phosphorus levels in the presence of depressed serum calcium levels, severe acidosis, anemia, and retarded growth, and illustrates many of the principles already discussed.

The differential diagnosis in cases of renal hyperparathyroidism lies between chronic nephritis, hyperparathyroidism (adenoma), cystic renal disease, obstructive uropathy, and diabetes insipidus.

In primary hyperparathyroidism, the serum calcium may be normal or elevated, while in secondary hyperparathyroidism, such as may occur from renal disease, the serum calcium may be normal or depressed. Parathyroid hyperactivity is not able to compete successfully with renal insufficiency.[15] The similarity to diabetes insipidus does not extend much beyond the symptoms of polydipsia and polyuria.

The presence of tetany is not frequent in this syndrome, largely because renal insufficiency results in chronic acidosis, which increase the ionization of calcium and, therefore, the availability of calcium.[17] This observation was confirmed in the case reported here.

SUMMARY

A case of renal hyperparathyroidism with osteitis fibrosa cystica secondary to congenital bilateral ureteral dilatation is presented.

The pathogenesis and certain aspects of the pathologic physiology involved in this syndrome are discussed.

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[15] Pappenheimer, A. M.: Effect of experimental reduction of kidney substance upon parathyroid glands and skeletal tissue. Jour. Exp. Med., 64: 965, 1936.

[16] Albright, F., Baird, P. C., Cope, O., and Bloomberg, E.: Studies on the physiology of the parathyroid glands. IV. Renal Complications of Hyperparathyroidism. Am. J. Med. Sci., 187: 49, 1934.

[17] Pincus, J. B., Peterson, H. A., and Kramer, B.: A study by means of ultrafiltration of the condition of several inorganic constituents of blood serum in disease. J. Biol. Chem., 68: 601, 1926.

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URETEROSUBARACHNOID ANASTOMOSIS FOR COMMUNICATING HYDROCEPHALUS

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Except for certain aspects of the operative procedure to be described herewith, the major portion of this paper is of interest primarily to the neurosurgeon. I believe that it is worthwhile, however, to bring the present subject to your attention because, as urologists, we are in the position of offering considerable help to our neurosurgical colleagues in the handling of certain selected cases of communicating hydrocephalus. An outline of the types of hydrocephalus and their respective pathology and treatment are shown in table 1.

The present discussion is not concerned with the noncommunicating type of hydrocephalus which is secondary to obstruction to pathways for the circulation of cerebrospinal fluid in the brain. Instead, we are interested in communicating hydrocephalus in which there is no obstruction to the flow of spinal fluid within the central nervous system but increased intracranial pressure and excessive amounts of cerebrospinal fluid occur because of impairment of reabsorption of spinal fluid from the subarachnoid space. This failure of reabsorption of fluid may be secondary to infection such as meningitis which was the cause in our first case, or much more commonly is congenital in nature. Rarely a child born with congenital communicating hydrocephalus will accommodate to the condition and live a normal life span. Such individuals are usually normal mentally and occasionally are geniuses, as was Napoleon. Neurosurgeons believe that if these infants can be tided over the first year or two of life, the chance of their accommodating to the condition is greatly enhanced. Without treatment, the vast majority of congenital hydrocephalics die in infancy.

By the injection of neutral phenolsulfonphthalein dye into a lateral ventricle of the brain, the neurosurgeon can differentiate precisely between noncommunicating and communicating types of hydrocephalus. If no dye appears subsequently in the spinal subarachnoid space, a noncommunicating or obstructive hydrocephalus is present. If dye does appear in the spinal subarachnoid space in from 10 to 30 minutes after injection, the hydrocephalus is of the communicating type and due to a defect or a block in the absorbing mechanism of the subarachnoid space. Normally, phenolsulfonphthalein injected in the subarachnoid space appears in the urine with normal excretion values being in the neighborhood of 40 per cent in the first two hours, 60 per cent in the first four hours, 80–90 per cent in the first twelve hours after injection. Excretion values in communicating hydrocephalus are in the range of 2–3 per cent, 5–10 per cent, and 20–25 per cent for these same time periods. In communicating hydrocephalus the operation of choice has been that of removal or destruction of the choroid plexus by various techniques in an effort to decrease the volume of spinal fluid

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Read at annual meeting, Southeastern Section, American Urological Association, Gulfport, Miss., February 2, 1950.

elaborated by this organ. The results, however, have not been very satisfactory. In 1925, Heile repeatedly attempted to anastomose the ureter directly to the spinal subarachnoid space but poor results were obtained due to ascending infection and cicatricial stenosis at the point of anastomosis. Many laboratory attempts and a number of efforts in the human have been made to provide an accessory area for absorption of spinal fluid in other parts of the body, including the subcutaneous tissue, the thoracic and peritoneal cavities, the thoracic duct, the intestines, the venous system, etc. None of these have proved successful.

Improvement in operative technique and supportive therapy, and particularly the introduction of polyethylene tubing of fine caliber, have made it possible to again attempt to utilize the ureter for draining off excessive amounts of spinal fluid in communicating hydrocephalus. Almost 3 years ago an 8 year old colored girl was admitted to Duke Hospital with post-traumatic pyogenic meningitis following an automobile accident. Through a bifrontal craniotomy incision, fracture fragments of the frontal sinus were removed and a massive dural defect repaired. With intrathecal penicillin therapy, the meningitis cleared in 19 days after craniotomy, and she appeared well. At this time, however, the frontal skull defect began to protrude and subsequent studies, including dye absorption tests and cerebellar craniotomy, disclosed the presence of a diffuse obliteration of the subarachnoid space with a resulting communicating hydrocephalus. Uretero-arachnoid anastomosis was carried out by Dr. Donald Matson, resident in neurosurgery, and myself, on April 30, 1947. The child's postoperative course was uneventful and the increased intracranial pressure was relieved as evidenced by depression instead of bulging of the cranial defect. Eighteen days after operation, a tantalum plate was inserted to close the defect in the frontal bone of the skull. Ten days later she was discharged, alert, active, and free of symptoms. At present, almost 3 years after operation, she is in excellent health.

TABLE 1. *Congenital hydrocephalus*

TYPE	PATHOLOGY	TREATMENT
A. Noncommunicating	1. Stenosis, aqueduct of Sylvius.	1. Choroid plexectomy
	2. Occlusion, foramina of Magendie and Luschka.	2. Third ventriculostomy.
	3. Tumor (rare)	3. Cerebellar exploration.
B. Communicating	1. Obliteration of subarachnoid space. a. Congenital ? b. Infectious ?	1. Choroid plexectomy.

Our handling of this and subsequent patients upon whom this procedure has been carried out has been as follows: After the diagnosis of communicating hydrocephalus has been made by the neurosurgeon and operation is decided upon, excretory urograms are obtained simply to be certain that two normally placed and functioning kidneys are present. To insure adequate fluid intake and blood replacement at the time of operation, phlebotomy has been done on infants on the evening before operation and a polyethylene cannula introduced into an ankle vein. Unless there is some contraindication, the left ureter has been chosen for the anastomosis because the left kidney is higher than the right and its ureter accordingly longer. Actually, however, I believe that the right ureter can be used equally as well. With the patient in position for operation upon the left kidney but tilted slightly forward, a left nephrectomy incision is made which extends well up in the costovertebral angle and nephrectomy performed (fig. 1). After ligation of the pedicle, the renal pelvis is dissected well up into the renal sinus and amputated from the kidney leaving a flare of renal pelvis attached to the upper ureter which facilitates subsequent suturing. The ureter is then calibrated with various sizes of polyethylene tubing and a proper caliber to fit the ureter snugly is selected. This is usually found to be about 6 to 8F in infants. The kidney incision is then lightly packed and a midline laminectomy incision is made with its center over the spinous process of the third lumbar vertebra. The previously selected polyethylene tube is then inserted through a small incision in the dura and arachnoid and directed downward for a distance of 3–4 cm. into the lower portion of the subarachnoid space Multiple small openings previously have been made in this portion of the tubing. A small nick is made in the side of the tubing at the point where it emerges from the dura and with a fine silk suture passed through the dura and tied around the tube at the point of the nick, it is securely anchored in place. The remaining defect in the dura is closed with interrupted silk. By blunt dissection with a clamp, a passageway is then made between the paravertebral muscle-

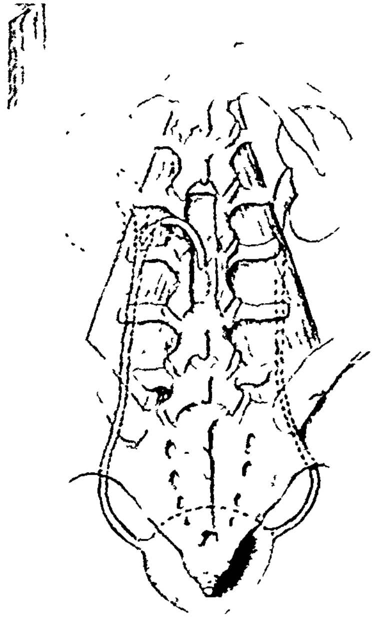

FIG 1. Schematic representation of left ureterosubarachnoid anastomosis. (Reprinted from the North Carolina Medical Journal, by permission of the editors.)

and the vertebral body from a point just above the transverse process of L-2 into the renal fossa, emerging here as a rule, just lateral to the lateral edge of the psoas muscle. The free end of the polyethylene tube is then drawn through this channel and inserted down the ureter for a distance sufficient to assure that its tip has traversed the abnormal curve thus produced in the upper ureter and lies in the normal ureteral axis without kinking. The fringe of renal pelvis attached to the upper ureter is then sutured to the fascia and muscle around the point where the polyethylene tube emerges into the renal fossa. The incisions are closed without drainage.

To date, 6 patients have been operated upon, one of these being 8 years old, the remaining 5 between 2 and 6 months of age.* Two have died within a month after discharge from the hospital apparently due to acute electrolyte depletion which resulted from the loss of large amounts of spinal fluid in the urine. The remaining 4 have had their diets supplemented with sodium chloride and are living and well; 1 for almost 3 years, 1 for 6 months, 1 for 5 months and one for 3½ months. With the exception of the first case, these children have been patients of, and operated upon by Dr. Barnes Woodhall, professor of neurosurgery, Duke Hospital. I wish to express my appreciation to Dr. Woodhall for permission to report these cases.

REFERENCE

WOODHALL, B. H.: Spinal subarachnoid ureteral anastomosis for communicating congenital hydrocephalus. N. C. Med. J., 10: 598-601, 1949.

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*Up to the time of publication, 6 additional patients have been operated on with no hospital deaths and apparently successful clinical results.

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SUPRAPUBIC TROCAR CYSTOSTOMY: AN EVALUATION AND PRESENTATION OF AN IMPROVED INSTRUMENT

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Trocar cystostomy is not new but is a procedure which I believe has not received the recognition or wide acceptance which it deserves. We have used it over a period of many years and have become convinced of its value and safety.

A technique for the operation was described by Lower in 1914, at which time he advocated its use especially for those patients with prostatic obstruction who could not be catheterized easily.[1] He first enunciated the important principle that a simple trocar cystostomy was preferable to and safer than a traumatic catheterization. Since this time several instruments for this purpose have been described but none, I believe, surpass the simple trocar principle suggested by Lower in his original article. Some refinements have been made possible by subsequent developments.

INDICATIONS

In general, the operation is indicated in any patient with chronic urinary retention in which a prolonged period of urinary drainage is necessary or desirable. First and foremost among these are the vesical neck obstructions, which include benign prostatic hypertrophy, vesical neck contracture, and carcinoma of the prostate. We have used the procedure for other conditions. The 400 cases which constitute the basis of the present review were divided as follows: 1) vesical neck obstruction, 337 cases (84.25 per cent); 2) neurogenic bladder, 35 cases (8.75 per cent); 3) urethral stricture, 15 cases (3.75 per cent); 4) for drainage in penile plastic operations, 3 cases (0.75 per cent); 5) others (carcinoma bladder, intractable cystitis), 10 cases (2.05 per cent).

Although the procedure has a rather wide application this discussion is concentrated on the cases in group 1 which is the most frequent type of disorder in which it is useful.

One must have an acceptable reason for advocating departure from a long accepted method of treatment. For many years, and even today in most places, the indwelling urethral catheter has been the accepted method for draining the chronically distended bladder. Some 10 years ago I studied a group of patients who died during the period of preoperative preparation for prostatic surgery and found that approximately 25 per cent died, perhaps unnecessarily, from urinary sepsis and uremia initiated by urethral instrumentation in which the indwelling catheter was the most common offender.[2] Even in patients who do not die, it is

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The author wishes to acknowledge the assistance of Dr. Thomas Uber of New Castle, Pa. and Dr. David McCune, Jr. of McKeesport, Pa. (former fellows in Urology), for statistical reviews of some of these cases.

[1] Lower, W. E.: *Trocar and cannula for suprapubic drainage of bladder.* Urol. & Cutan. Rev., **18:** 6, 1914.

[2] Engel, W. J.: *Preoperative prostatic mortality.* J. Urol., **41:** 505, 1939.

Read at annual meeting, Southeastern Section, American Urological Association, Gulfport, Miss., February 2, 1950.

a common experience to observe chills or fever and a period of febrile illness coming on a few days after inserting an indwelling catheter. The resultant illness causes debility, prolongs the patient's period of morbidity and, in my opinion, renders him a less favorable risk for prostatic surgery. It was to prevent this mortality and morbidity and to increase the safety and comfort of preparing the patient for operative relief of the bladder neck obstruction that we turned to trocar cystostomy. In the period of 10 years, I have reviewed 400 cases handled in this manner and this experience forms the basis of the present report.

Not all patients require cystostomy drainage, so one must first establish the criteria which call for this procedure. This requires a careful history and physical examination, with particular emphasis on the cardiovascular system to determine if there is any complicating systemic disease which may demand temporary drainage and postponement of prostatic surgical intervention. Among such conditions we have encountered coronary thrombosis, arteriosclerotic heart disease with decompensation, cerebral thrombosis or hemorrhage, and concomitant gastro-intestinal malignancy as worthy of mention.

Having considered complicating disease outside the urinary tract, the next concern is with the status of the urinary tract. Preliminary urinalysis may indicate the presence of infection and a persistently low specific gravity makes us mindful of impaired renal function. A blood urea determination is done in all cases and if this is below 60 mg. per cent we then routinely do an excretory urogram. From this[3] one determines not only the functional ability of the kidneys but equally important the anatomic status of the upper urinary tract. Delayed function with bilateral hydro-ureter and hydronephrosis calls for a period of preoperative drainage, even though the urea may not be significantly elevated.

Trocar cystostomy is thus indicated in patients with vesical neck obstruction who require a period of preoperative drainage because of: 1) chronic urinary retention with large palpably distended bladder; 2) an elevated blood urea or creatinine as an indication of renal failure; 3) delayed function with bilateral hydronephrosis with hydroureter demonstrated by excretory urogram; 4) patients in whom operation must be deferred because of complicating disease.

It should be emphasized that these factors may be determined without any urethral instrumentation.

TECHNIQUE

The instrument is shown in figure 1. It consists of a trocar which is pointed but not needle-sharp, which fits snugly into the cannula which is made with a finger grip at the top. This cannula will admit an 18 or 20F bag catheter or straight catheter if preferred. It also admits the right angle observation telescope which is used with the McCarthy resectoscope. A water tight connection is afforded by means of an adapter which fits snugly into the top of the cannula and through which the telescope passes as shown in *B*, a photo of the assembled instrument. The only other instruments required are a syringe and needle for local anesthesia, a scalpel and a piece of silk suture on a cutting needle to approximate the skin and secure the catheter with a tie. The patient is placed in the supine position in a slight head down position if possible. In the majority of instances the bladder will be palpable from retained urine, but if not, it should be made palpable by distention with sterile saline solution. Caution dictates that the procedure should not be carried out unless the bladder is clearly palpable.

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[3] Engel, W. J.: Intravenous urography in study of vesical neck obstructions. Am. J. Roentgenol., 62: 661, 1949.

After painting the skin with an antiseptic solution, the field is draped with sterile linens. We have generally used local or intravenous pentothal anesthesia, but I would advise against the latter in the presence of severe renal damage. If local anesthesia is used, a small cutaneous wheal is raised in the midline, 2 fingers' breadth above the symphysis. With a longer needle attached to the syringe, the proposed tract is injected with a small amount of novocain and the needle advanced until urine can be aspirated. This establishes the line along which the trocar shall be introduced later and an estimate of the depth to which it must be plunged. A small transverse midline incision is made just large enough to admit the trocar easily. This instrument should be grasped firmly in the right hand in such a manner as to permit an auger-like rotating wrist motion. With this motion the trocar and cannula are then plunged briskly into the bladder along the tract previously determined by the aspirating needle. Entrance into the bladder will be recognized by a sudden sensation of having "popped" into a free space. The auger-like motion seems to be important, as it greatly facilitates introduction.

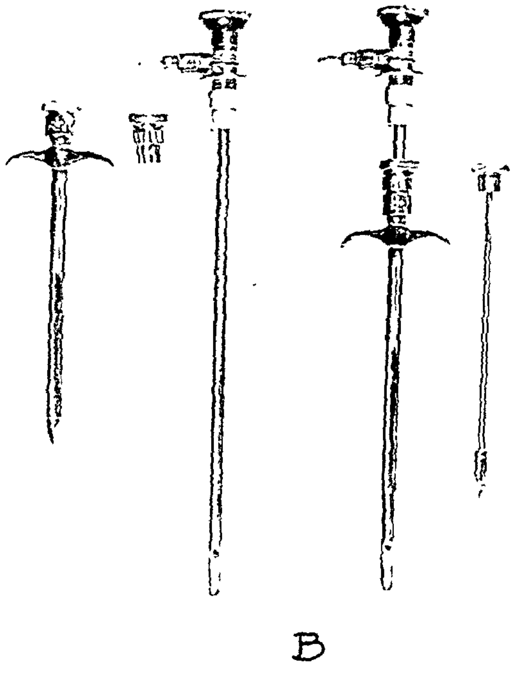

FIG. 1. *A*, trocar and cannula, adaptor and telescope. *B*, cannula with telescope in place for viewing bladder and vesical neck. Right angle telescope with light is same as used with resectoscope.

minimizes the chance of pushing the bladder ahead of the instrument, and tends to separate rather than cut tissues through which it passes. I think the latter is a significant factor in preventing leakage because of the resulting snug fit around the catheter.

Having entered the bladder, the trocar is removed and the telescope and adapter are quickly introduced through the cannula and with the light cord attached, one can make a careful inspection of the bladder and vesical neck. One obtains a complete bladder's-eye view of the vesical neck, which is not only interesting and instructive, but permits an accurate judgment of the type of operation necessary to later relieve the obstruction. Visualization is carried out through the medium of the patient's own urine. Occasionally this is cloudy from infection. When this situation is encountered we have preferred to abandon cystoscopic visualization rather than to subject the patient to the danger of leakage by attempting repeated irrigation through the cannula.

If cloudy infected urine is known to exist, it is permissible to irrigate the bladder by a urethral catheter immediately preceding the cystostomy, following which the bladder is fully distended with clear saline solution.

Having completed the cystoscopic inspection, the telescope is removed and a No. 18 or 20, 5 cc bag catheter is quickly introduced into the bladder through the cannula. One must be sure that more than enough catheter is introduced to permit withdrawal of the cannula without the danger of pulling out the catheter. (If the standard bag catheter is used it is usually necessary to cut off the expanded bell to permit it to be drawn through the cannula.) The bag is then distended. As an added safeguard, a silk suture is passed through the margins of the incision, tied, and then securely tied around the catheter to prevent accidental pulling out of the catheter. A small dressing is applied and then one may support the catheter further with adhesive if still pessimistic about accidental withdrawal.

We do not believe that it is necessary to decompress bladders drained in this manner. In a few cases we have seen a slight bloody tinge to the drainage as a result of vascular congestion which follows sudden emptying, but no serious complications have been observed.

CARE OF THE CATHETER

Once in place, the catheter should not be disturbed for a period of about 5 days, provided it is draining satisfactorily. At the end of that time the silk suture may be cut and the bag drawn up against the dome of the bladder. Attempt to change the suprapubic catheter before 5 days is not recommended. It requires that much time for a sinus tract to form and we have failed in attempts to reintroduce the catheter after three and four days.

The catheter should be changed at intervals of 2 to 3 weeks to prevent incrustation. If deemed advisable, the size of the catheter may be increased one size at each change. For example, an 18F may be replaced with a 20F, and this, in turn, with a 22F, and so on. We have carried this up to a 24F but there is generally no purpose served by the larger sizes which will not be accomplished with a 20 or 22F.

The patient may be up and about immediately if he so desires. In most cases a period of 6 to 8 weeks of drainage is desirable before undertaking an operation upon the prostate. Provided that progress is satisfactory, we usually permit the patient to return to familiar home surroundings after 5 to 7 days. In the last 100 cases, 92 per cent have been allowed to go home. This is an economic saving to the patient, releases hospital beds for which there appears to be an ever-increasing demand, and we believe that the patients do better at home. They are instructed to plug their catheters during the day and may be about as much as they please. Many have returned to their regular work without inconvenience. At night, continuous drainage to a bottle permits uninterrupted sleep. Irrigation of the catheter is not essential but daily lavage with 1:5000 potassium permanganate is usually recommended to insure patency of the lumen.

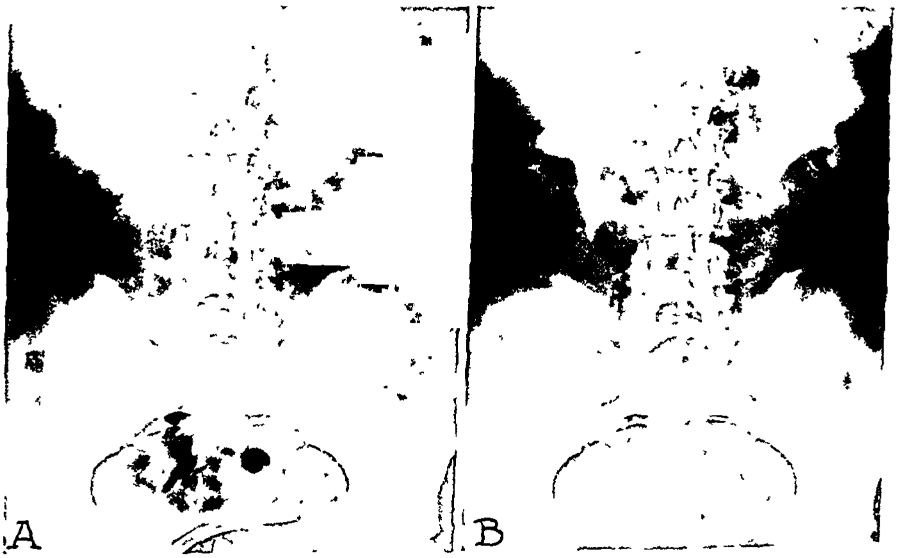

FIG. 2. *A*, excretory urogram before trocar cystostomy showing marked bilateral hydronephrosis resulting from chronic urinary retention. *B*, urogram on same patient 6 weeks after suprapubic drainage established by trocar cystostomy.

At each return visit for change of catheter, the blood urea is repeated and when a normal level is reached the patient is considered for prostatic surgery. The general condition of the patient must have improved and this is determined not only by his appearance but by increased strength, vigor, improved appetite and usually some weight gain. A recheck urogram is generally done and improved renal function established by prompt and adequate excretion of the dye and reduction in the degree of hydro-ureter and hydronephrosis (fig. 2). In this condition the patient is ready for any type of prostatic operation which may be indicated.

If transurethral resection is done, the presence of the suprapubic catheter provides a useful means of accelerating the operation. By allowing the irrigating fluid to flow in through the resectoscope and out through the suprapubic catheter, a continuous flow is established. In this maneuver the bladder should first be gently distended by compressing the suprapubic tube and then the outflow regulated to equal or approximate the rate of inflow. Much time is saved by avoiding the necessity of discontinuing the operation to empty the bladder, as is required with the intact bladder.

Following transurethral resection it is our custom to introduce the usual urethral bag catheter and the suprapubic catheter is then removed in about 24 hours if the risk of significant bleeding has passed. It is rare indeed for the suprapubic sinus to drain for more than a few hours and we have never seen a permanent fistula remain even in patients who have worn their catheters for months. Three to four days later the urethral catheter is removed.

Complications have not been numerous or of serious consequence. Urologic colleagues frequently express fear of traversing the peritoneal cavity or possible injury to the bowel. We have never observed peritonitis at autopsy nor has the clinical course of the patient ever caused this diagnosis to be entertained. In our experience, if the bladder is adequately distended, the peritoneal reflection is high enough to be out of the path of the trocar. Furthermore, Ferrier[4] did bladder paracentesis on 50 cadavers after distention to 500 cc and in no case was the peritoneum touched.

This situation may not obtain in patients who have suprapubic scars from previous cystostomy or other pelvic operations and we consider such scars as contraindications to the use of the procedure. One of my associates reports entering the bowel in a patient who had had a previous combined abdominoperineal resection for rectal cancer, and while no ill effects resulted, it illustrates the potential danger in such cases.

The complication or technical error which we have come to regard with greatest concern is that of having the suprapubic tube come out or be pulled out either at the time of operation or in the first 24 to 48 hours before an adequate sinus tract has had time to form. This may result in perivesical extravasation and infection which occurred in 3 of our fatal cases. In several instances we have carried out an immediate repeat trocar cystostomy with success when it was not possible to replace a catheter which had come out.

Significant bleeding as the result of introducing this trocar has never been observed. Moderate hematuria ascribed to sudden emptying of the bladder is not infrequent but does not have serious consequences.

Febrile reaction in patients who have not had previous urethral instrumentation is exceptional. This is one reason for urging that trocar cystostomy should be the initial procedure whenever possible. Too often we have been obliged to resort to trocar cystostomy after the patient has experienced a severe reaction to an indwelling catheter. Time is lost thereby and much of the advantage of trocar drainage is sacrificed. Acute urinary retention should be managed by intermittent catheterization until adequate study determines the necessity for an extended period of drainage, in which case trocar cystostomy should be done immediately.

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[4] Ferrier, P A Personal communication to R. W. Barnes. Endoscopic Prostatic Surgery. St. Louis: C. V. Mosby Co , 1943, p. 77.

MORTALITY

It must be remembered that this procedure, by its very nature, will be used in many superannuated or desperately bad risk patients with advanced renal failure or associated disease in other organs and systems in which a fatal outcome cannot properly be charged to the operation. Among these may be mentioned coronary occlusion, advanced carcinoma of the prostate with metastasis, cancer in other organs, notably bladder, colon and rectum, and irreversible uremia. Thirteen such cases occurred in the present series. These are summarized in table 1. In many of these the interval between cystostomy and death was well beyond the time it reasonably could be attributed to the operation.

TABLE 1. *Trocar cystostomy; 13 deaths not attributable to operation*

CAUSE OF DEATH	CASES	DAYS BETWEEN OPERATION AND DEATH	PATIENT'S AGE
Advanced carcinoma of bladder	1	136	79
Coronary occlusion or advanced heart disease	4	18	65
		14	80
		21	69
		4	77
Carcinoma of prostate advanced with metastases	2	37	86
		51	67
Carcinoma of rectum	1	19	80
Advanced uremia, anemia, etc.	2	4	87
		90	69
Pneumonia	1	13	71
Disease of central nervous system, myelitis, meningioma	2	11	38
		2	68
Total . .	13		
Average age (excluding neurogenic cases)			75.45 years

TABLE 2 *Trocar cystostomy mortality; 9 deaths in 400 operations, 2.25 per cent*

	CASES	DAYS FROM OPERATION TO DEATH	AGE
Technical imperfections, catheter did not drain properly or pulled out	4	11	64
		10	77
		9	86
		4	75
Trocar cystostomy not done primarily Preliminary indwelling catheter with fever and pyelonephritis	3	8	87
		4	77
		1	76
Unavoidable complication	2	3	76
Cerebral thrombosis			
Carcinoma of prostate—cardiac failure		5	86
Average age			77.1 years

There were 9 deaths in which the train of events from operation to death indicated the procedure as having been causative. These are summarized in table 2, in which the cases are broken down to indicate the factors which contributed to the unfavorable outcome. In this connection, attention is drawn to the age of the patients, the average age being 77.1 years. The group of 4 in which the suprapubic tube came out or did not drain are considered to be technical imperfections and these have been corrected recently for the most part. In 3 cases trocar cystostomy was performed after urinary sepsis had complicated the introduction of an indwelling urethral catheter. The difficulties encountered in this group may be avoided by employing trocar cystostomy as the initial procedure.

COMMENTS AND CONCLUSIONS

Our enthusiasm for suprapubic trocar cystostomy should not convey the impression that it should be used indiscriminately. We believe that it is the procedure of choice in patients with vesical neck obstruction in whom chronic urinary retention has impaired renal function to the point where prolonged drainage is required. Definite criteria for selecting these should be followed.

The bladder must be palpably distended in order to permit the procedure to be carried out safely. Decision to do trocar cystostomy should be made immediately after completing the original necessary examinations and, if elected, it should be the first procedure. Many of its advantages are lost if it is brought to the patient who has first been subjected to indwelling catheter drainage which has provoked a urinary sepsis. For the patient who needs it, trocar cystostomy is less hazardous than the indwelling catheter and, as Dr. Lower indicated long ago, it is much safer than a traumatic catheterization.

The present instrument which permits thorough cystoscopic inspection of the bladder permits a determination of the exact type of vesical neck changes and type of operation later required for its correction.

In properly selected cases we believe its use adds a considerable factor of safety and comfort to the potentially dangerous period of preparation for the operation later required.

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URETEROSIGMOIDOSTOMY: A COMPARATIVE STUDY OF TECHNIQUES

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Recent years have brought forth a revival of the use of uretero-intestinal anastomosis in the treatment of certain conditions and the indications for its employment appear to be continually widening. In the main these latter are: 1) complete exstrophy of the bladder, 2) intractable vesicovaginal fistula, 3) certain vesical malignancies, 4) extensive injuries to the bladder and/or posterior urethra which make retention of urine impossible, 5) palliative diversion of the urinary stream in instances of intractable contracted urinary bladders with varying associated conditions.

Thomas Smith (1878) of England is credited with the first transplantation of the ureters into the large bowel. Since that time 80 to 85 techniques have been recommended and successfully used by many surgeons. The very number of methods, however, as well as the profuseness of dissertations on the subject, attests to the reality that an ideal procedure has not been devised.

In 1911, Robert Coffey introduced the first of his three techniques using submucous tunnels and it is the fundamental principles of his methods which, with variations and adaptations, have been used in most of the subsequent techniques. Emphasis is placed on the construction of a submucous tunnel (length variable) in the bowel wall through which the ureter passes before entering the lumen of the intestine. Supposedly the conduction of feces towards the rectum exerts pressure against the ureteral opening thereby producing a valve-like action.

Recently Cordonnier, utilizing the fundamentals of a principle described by Chaput in 1896, presented a type of uretero-intestinal anastomosis which eliminates the submucous tunnel and accurately approximates the ureteral mucosa to the mucosa of the bowel. This method is said to produce exactly the ureterocloacal arrangement as in fowls and to lessen the occurrence of postoperative stenosis with poor drainage and subsequent hydronephrosis which not infrequently follows the use of the tunnel technique.

At Lawson V. A. Hospital, until 3 months prior to this writing, all uretero-intestinal anastomoses were done by techniques involving the use of the submucous tunnel. In our earliest cases we used an incision approximately 6 to 7 cm. in length in the bowel wall; later cases were done with a trough 2.5 to 3 cm. in length. Three months ago we started using the technique suggested by Cordonnier. It is not our purpose here to analyze all our cases in detail, as this is being prepared for publication at a later date. Rather, we desire to show in this preliminary report the generally marked differences in the postoperative

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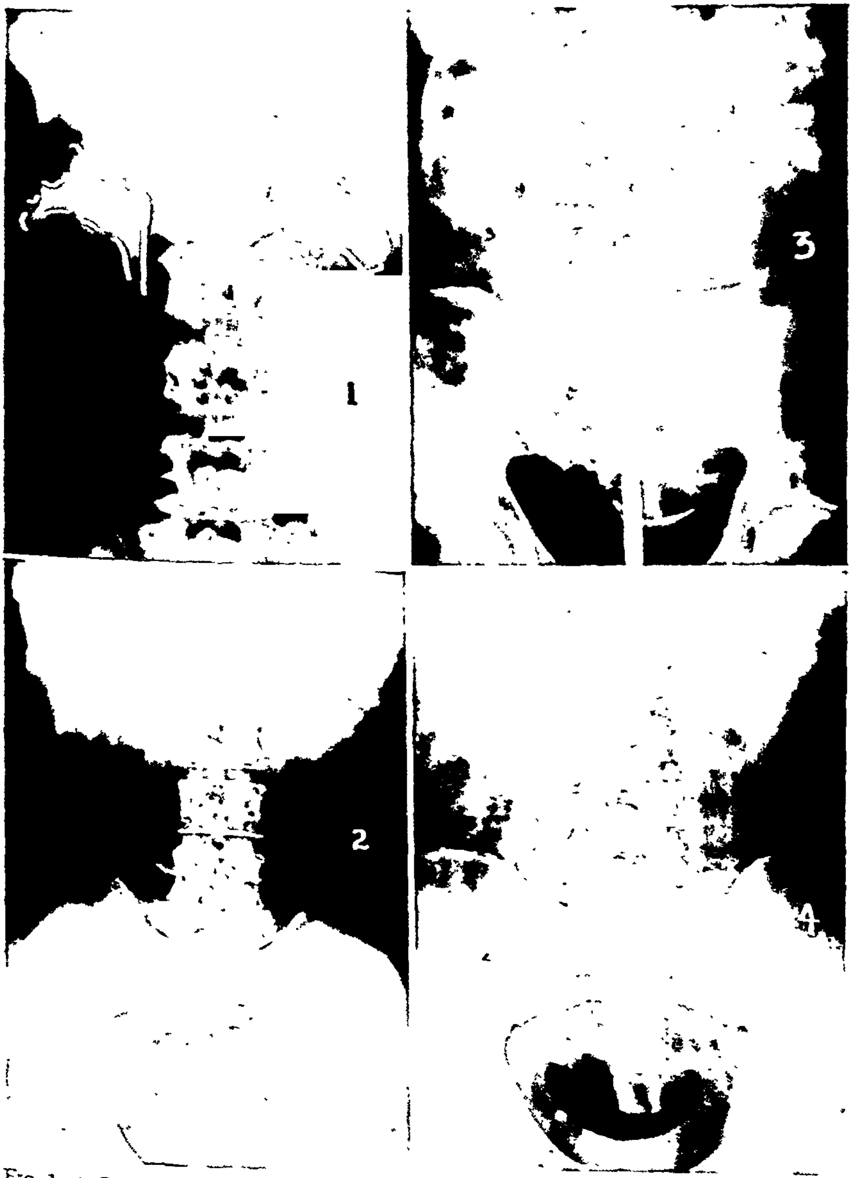

Fig. 1. *1.* Case 1. Bilateral ureterosigmoidostomy, one stage. Long submucous tunnel. First 24 hour output, 65 cc. Mild early pyelonephritis.
2. Case 2. Bilateral ureterosigmoidostomy, one stage. Long submucous tunnel. First 24 hour output 250 cc. Mild early pyelonephritis.
3. Case 3. Bilateral ureterosigmoidostomy, one stage. Long submucous tunnel. First 24 hour output 45 cc Moderate early and late pyelonephritis.
4. Case 4. Bilateral ureterosigmoidostomy, one stage. Long submucous tunnel. First 24 hour output, 400 cc. Mild delayed pyelonephritis.

results, both clinically and urographically, in cases where the three different techniques have been used. To do this as concisely as possible, we have arbitrarily

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From the Department of Urology, Lawson V. A. Hospital and Emory University School of Medicine, Atlanta, Ga.

Recent years have brought forth a revival of the use of uretero-intestinal anastomosis in the treatment of certain conditions and the indications for its employment appear to be continually widening. In the main these latter are: 1) complete exstrophy of the bladder, 2) intractable vesicovaginal fistula, 3) certain vesical malignancies, 4) extensive injuries to the bladder and/or posterior urethra which make retention of urine impossible, 5) palliative diversion of the urinary stream in instances of intractable contracted urinary bladders with varying associated conditions.

Thomas Smith (1878) of England is credited with the first transplantation of the ureters into the large bowel. Since that time 80 to 85 techniques have been recommended and successfully used by many surgeons. The very number of methods, however, as well as the profuseness of dissertations on the subject, attests to the reality that an ideal procedure has not been devised.

In 1911, Robert Coffey introduced the first of his three techniques using submucous tunnels and it is the fundamental principles of his methods which, with variations and adaptations, have been used in most of the subsequent techniques. Emphasis is placed on the construction of a submucous tunnel (length variable) in the bowel wall through which the ureter passes before entering the lumen of the intestine. Supposedly the conduction of feces towards the rectum exerts pressure against the ureteral opening thereby producing a valve-like action.

Recently Cordonnier, utilizing the fundamentals of a principle described by Chaput in 1896, presented a type of uretero-intestinal anastomosis which eliminates the submucous tunnel and accurately approximates the ureteral mucosa to the mucosa of the bowel. This method is said to produce exactly the ureterocloacal arrangement as in fowls and to lessen the occurrence of postoperative stenosis with poor drainage and subsequent hydronephrosis which not infrequently follows the use of the tunnel technique.

At Lawson V. A. Hospital, until 3 months prior to this writing, all uretero-intestinal anastomoses were done by techniques involving the use of the submucous tunnel. In our earliest cases we used an incision approximately 6 to 7 cm. in length in the bowel wall; later cases were done with a trough 2.5 to 3 cm. in length. Three months ago we started using the technique suggested by Cordonnier. It is not our purpose here to analyze all our cases in detail, as this is being prepared for publication at a later date. Rather, we desire to show in this preliminary report the generally marked differences in the postoperative

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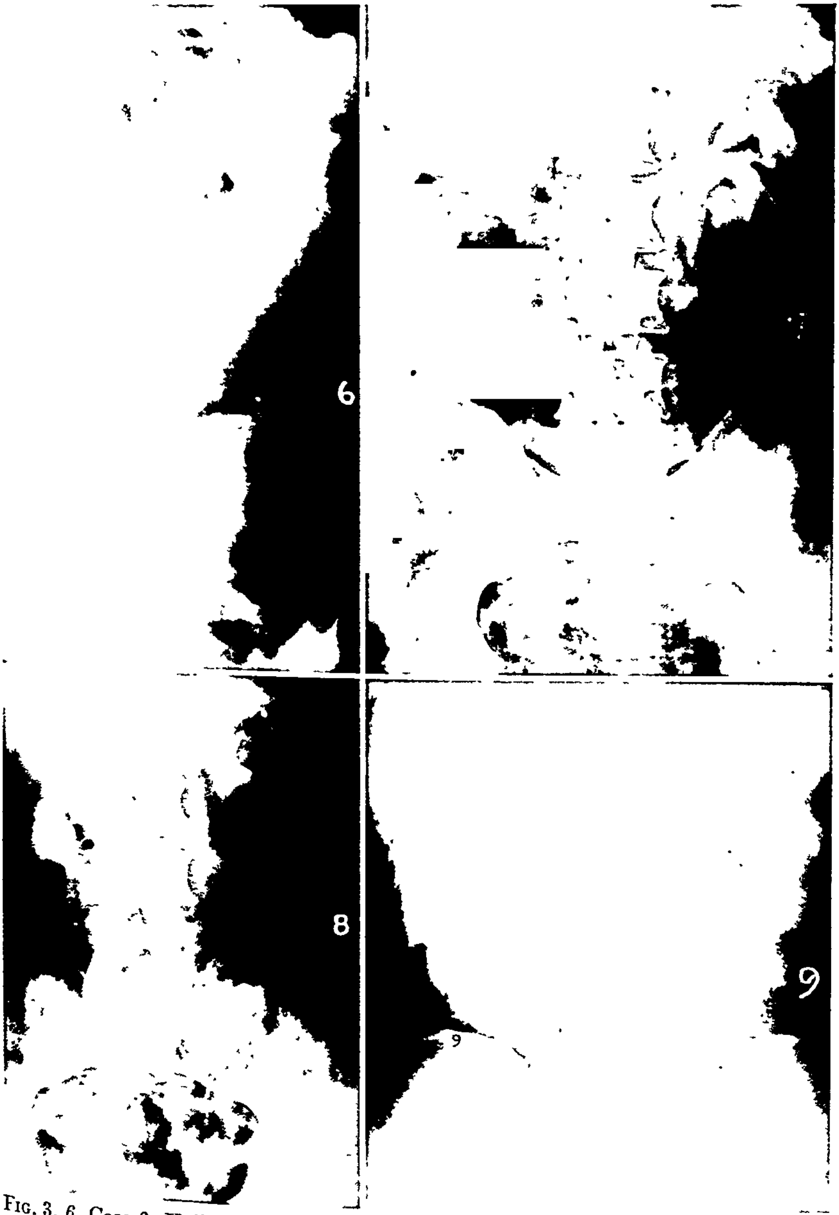

FIG. 3. *6*, Case 6. Unilateral ureterosigmoidostomy. Short submucous tunnel. First 24 hour output, 250 cc. Delayed severe pyelonephritis.

7, Case 7. Bilateral ureterosigmoidostomy, one stage. Short submucous tunnel. First 24 hour output, 1800 cc. No clinical evidence of pyelonephritis.

8, Case 8. Bilateral ureterosigmoidostomy, one stage. Short submucous tunnel. First 24 hour output, 1500 cc. Delayed mild pyelonephritis.

9, Case 9. Bilateral ureterosigmoidostomy, one stage. Short submucous tunnel. First 24 hour output, 860 cc. No clinical evidence of pyelonephritis.

selected the first 5 cases done by each technique and have reproduced the postoperative urograms. A short clinical note accompanies each illustration.

The latest operative technique consists of a transperitoneal approach to the ureters which are freed from their bed for only a short distance (3 to 4 cm.) in order to preserve the blood supply. Anastomoses are made at the most proximal points in the sigmoid colon, this latter being brought to the ureters and then fixed. Mucosa is accurately approximated to mucosa and then the serosa of the bowel and adventitia of the ureter are likewise sutured. Care is taken to keep the ureters as straight as possible and thus refrain from interrupting normal peristaltic waves. The sites of the anastomoses are extraperitonealized in all cases. Postoperatively a rectal tube is inserted and is left in place 5 days. Often this needs changing or manipulation to overcome "pooling" of urine in the rectum. The patient is kept on intravenous fluids, fortified with heavy doses of vitamins C and B-complex, for 3 days after which a low residue diet is instituted for approximately 1 week. Wangensteen duodenal suction is used when indicated and is used routinely in the young and old age groups. Postoperative administration of vitamins C, B and K is important. The use of sulfasuxidine for a 5 day course preoperatively and for an indefinite period postoperatively is a routine procedure.

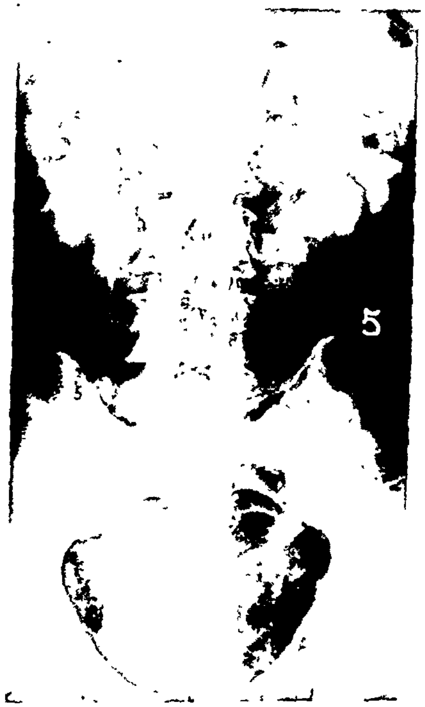

FIG. 2. Case 5. Bilateral ureterosigmoidostomy, one stage. Long submucous tunnel First 24 hour output, 1100 cc. Delayed moderate pyelonephritis.

Briefly, a review of our urographic and case data, as exemplified by figures 1–5, indicates that the accurate approximation of ureteral mucosa to intestinal

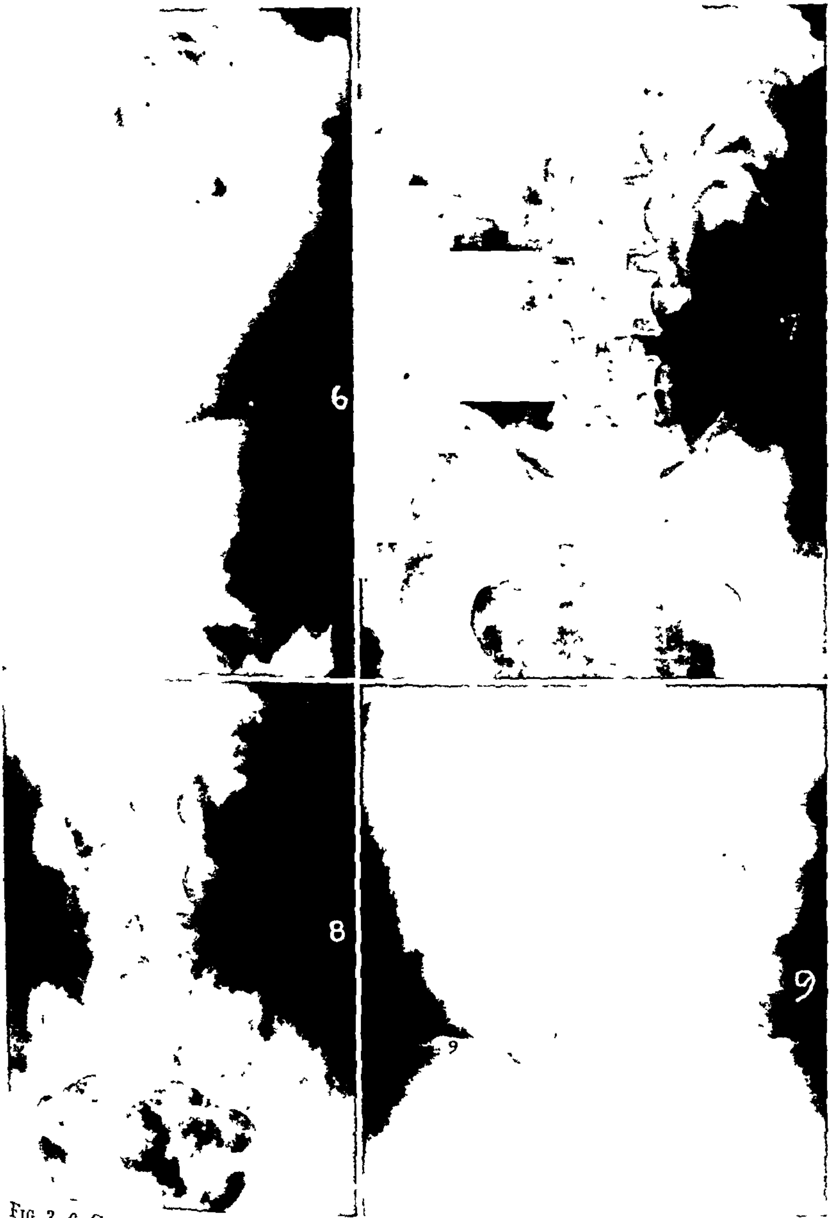

FIG. 3. 6, Case 6. Unilateral ureterosigmoidostomy Short submucous tunnel. First 24 hour output, 250 cc. Delayed severe pyelonephritis.

7, Case 7. Bilateral ureterosigmoidostomy, one stage Short submucous tunnel. First 24 hour output, 1800 cc. No clinical evidence of pyelonephritis.

8, Case 8 Bilateral ureterosigmoidostomy, one stage. Short submucous tunnel. First 24 hour output, 1500 cc. Delayed mild pyelonephritis

9, Case 9. Bilateral ureterosigmoidostomy, one stage. Short submucous tunnel. First 24 hour output, 860 cc. No clinical evidence of pyelonephritis.

(sigmoid colon) mucosa in carrying out the procedure of ureterosigmoidostomy effected a superior end result both anatomically and clinically to that obtained in most instances when a submucous tunnel was used. There is a direct ratio between the degree of dilatation of the ureters, pelves and calyces and the length of the submucous tunnel. Generally speaking, ectasia was comparatively greater where a long trough was utilized; less in those in which a short trough was used; and least in those instances where the tunnel was eliminated. The same ratio holds true with regards to ascending infection, both early and late, while it is reversed in relation to the output of urine in the first 24 hours. Table 1 shows average output in each group for the first 24 hours and table 2 reveals the incidence of early (within 2 weeks postoperatively) and late clinical pyelonephritis.

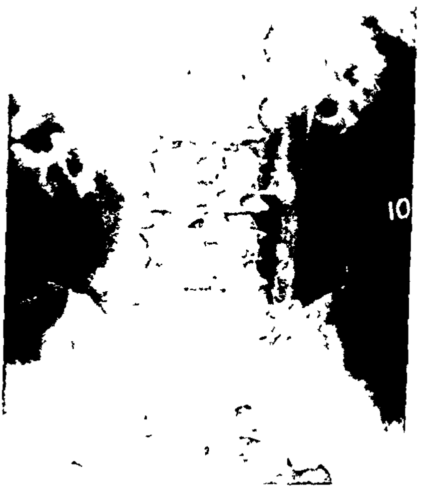

FIG. 4. Case 10. Bilateral ureterosigmoidostomy, one stage. Short submucous tunnel. First 24 hour output, 1480 cc. Delayed mild pyelonephritis.

TABLE 1. *Average output during the first 24 hours*

Long submucous tunnel	370 cc
Short submucous tunnel	1180 cc
Mucosa to mucosa anastomosis	2100 cc

TABLE 2. *Incidence of early and delayed clinical pyelonephritis (number of cases)*

	EARLY PYELONEPHRITIS	DELAYED PYELONEPHRITIS	COMBINATION OF EARLY AND DELAYED	NO CLINICAL PYELONEPHRITIS
Long submucous tunnel	2	2	1	
Short submucous tunnel	0	3	0	2
Mucosa to mucosa anastomosis		1*		1

* Pyelonephritis occurred on the right side which was anastomosed by short tunnel technique.

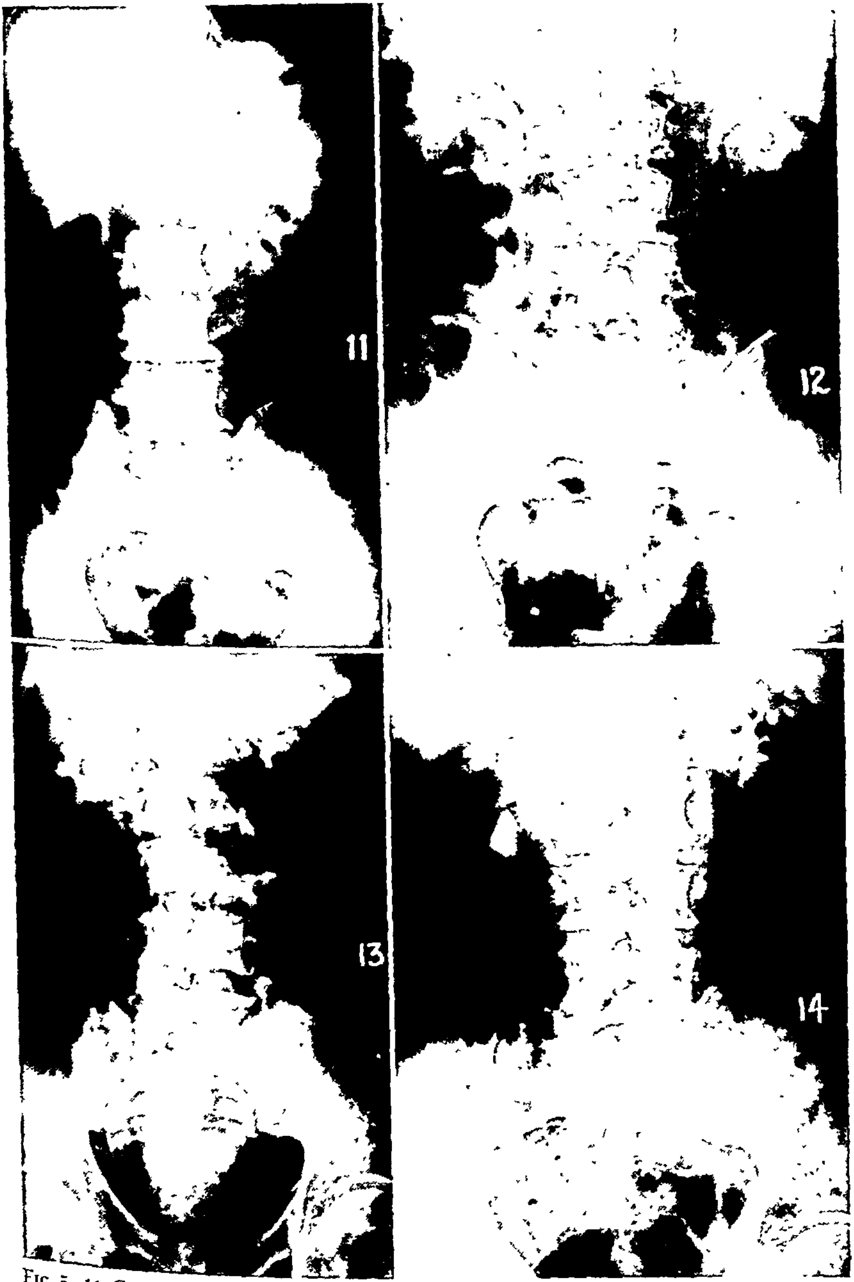

FIG. 5. *11*, Case 11. Bilateral ureterosigmoidostomy, one-stage. Mucosa to mucosa anastomosis. First 24 hour output, 2300 cc. No clinical evidence of pyelonephritis.
12, Case 12. Bilateral ureterosigmoidostomy, one-stage. Mucosa to mucosa anastomosis. First 24 hour output, 2800 cc. No clinical evidence of pyelonephritis.
13, Case 13. Bilateral ureterosigmoidostomy, one-stage. Mucosa to mucosa anastomosis. First 24 hour output, 2200 cc. No clinical evidence of pyelonephritis.
14, Case 14. Bilateral ureterosigmoidostomy, one stage. Mucosa to mucosa anastomosis. First 24 hour output, 1790 cc. No clinical evidence of pyelonephritis.

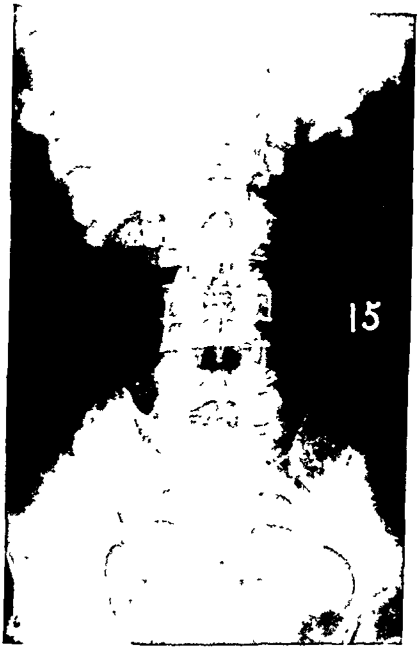

Fig. 6. Bilateral ureterosigmoidostomy, one-stage. Mucosa to mucosa on left side; short tunnel on right. First 24 hour output, 1400 cc. *Mild delayed pyelonephritis. (Two techniques* were utilized here for demonstration purposes for a medical motion picture.)

SUMMARY

A comparative study of techniques in the procedure of uretero-sigmoidostomy has been presented.

REFERENCE

Cordonnier, J. J.: Surg., Gynec. & Obst., 88: 441, 1949.

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FURTHER OBSERVATIONS ON THE ELECTROLYTE PATTERN OF THE BLOOD AFTER BILATERAL URETEROSIGMOIDOSTOMY

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At the last regular session of the Section of Urology of the American Medical Association (1949), two of us (Ferris and Odel) reported on some of our experiences with a group of cases in which abnormalities in the electrolyte pattern of the blood developed after bilateral ureterosigmoidostomy.[1] The characteristic abnormality which develops in such patients is hyperchloremic acidosis, associated with azotemia and dehydration. In a series of 141 patients who underwent bilateral ureterosigmoidostomy between the years 1939 and 1949, 79 per cent manifested some degree of hyperchloremia at some period after their operations, and 80 per cent showed laboratory evidence of acidosis of some degree as manifested by values for the carbon dioxide combining power of the plasma of less than 22 milliequivalents of bicarbonate per liter.

PRESENT STUDY

Since that time we have had the opportunity of conducting a more detailed study on one of these patients, the results of which we wish to report on at this time.

The patient, a man aged 25 years, registered at the Mayo Clinic September 11, 1948. One of us (Priestley) had performed bilateral ureterosigmoidostomy on this patient 9 years previously when he was 16 years old. He had progressed satisfactorily after this operation until 2 years before admission when he had begun to experience backache and recurrent episodes of chills and fever. In addition, he reported at that time that for several months he had had no appetite, had had frequent nausea and vomiting and diarrhea with rectal incontinence, particularly during the night, unless he arose to "defecate" at hourly intervals. At the time of examination at the clinic he was found to have severe hyperchloremic acidosis (table 1) and bilateral renal calculi. His diet was made low in chloride (table 2) with the addition of 4 gm. of sodium bicarbonate daily for the purpose of replacement of sodium. Nine days later, although he still manifested laboratory evidence of mild hyperchloremia and acidosis, his nausea and vomiting had disappeared, polyuria and polydipsia had decreased, and he was able to sleep through the night without having to get up to "defecate." After correction of the acidosis, right nephrolithotomy was performed on October 19, 1948, after which a nephrostomy tube was left in place for 13 days. During this

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hershey, Pa., May 24, 1950.

[1] Ferris, D. O. and Odel, H. M.: Electrolyte pattern of the blood after bilateral ureterosigmoidostomy. J. A. M. A., 142: 634–641, 1950.

period the patient received a normal diet without restriction of sodium chloride, and all urine recovered from the nephrostomy tube was saved for determination of chloride (table 3). As soon as the nephrostomy tube was removed, the patient's diet again was made low in chloride (table 2), and at the time of dismissal he was instructed to follow the same diet with the addition of sodium bicarbonate in a dose of 1.3 gm. daily.

TABLE 1. *Chemical composition of the blood; first observation*

DATE	MILLIGRAMS PER 100 CC OF BLOOD		MILLIEQUIVALENTS PER LITER OF PLASMA OR SERUM		
	Urea	Creatinine	Chloride	Bicarbonate	Sodium
Normal values	40 or less	2 or less	103	27	142
3-27-39	Bilateral ureterosigmoidostomy				
3-30-39	46		114	19	
9-11-48	102	2.7	121	13	139
9-14-48	Low chloride diet plus $NaHCO_3$ 1.3 gm. three times a day				
9-20-48	104	2.8	108	20	143
9-24-48	110	2.8	107	18	141
10-2-48	74	2.4	107	27	123
10-8-48	66		102	29	139
10-19-48	Right nephrostomy; normal diet				
10-20-48	116	2.4	116	20	
10-21-48	126	3.0	106	21	
10-23-48	96	2.6	99	23	
10-25-48	96	2.7	98	21	
10-27-48	90	1.4	100	26	
10-29-48	Low chloride diet plus $NaHCO_3$ 1.3 gm. daily				
10-30-48	56		100	24	
11-1-48	Nephrostomy tube removed				
11-2-48	72		102	28	
11-8-48	72	2.8	96	32	

TABLE 2. *Low chloride diet**

CONSTITUENTS	AMOUNTS
Protein	75 gm.
Carbohydrate	260 gm.
Fat	110 gm.
Calories	2,300 gm.
Sodium	1.6 gm.
Chlorine	2.2 gm.
Calcium	0.9 gm.
Iron	0.013 gm.

* Diet is adequate in all vitamins according to recommended allowances of the National Research Council.

The patient returned to the clinic April 20, 1949, at which time he had gained 29 pounds (13 kg.) and was entirely free from symptoms. Study of the electrolytes was begun on April 20 and continued through June 4 (forty-six days). The

TABLE 3. *Chloride in urine recovered from right nephrostomy tube*

DATE, 1948	VOLUME, CC	CHLORIDE IN URINE*	
		Total mg.	Mg. per 100 cc
Normal values			400–600
10-22	56	430	770
10-23	210	430	900
10-25	225	420	950
10-26	178	430	760
10-27	47	470	580
10-28	57	490	280
10-29	70	500	350
10-30	64	540	350
11-1	115	440	510
11-2	100	420	420

* Expressed as NaCl.

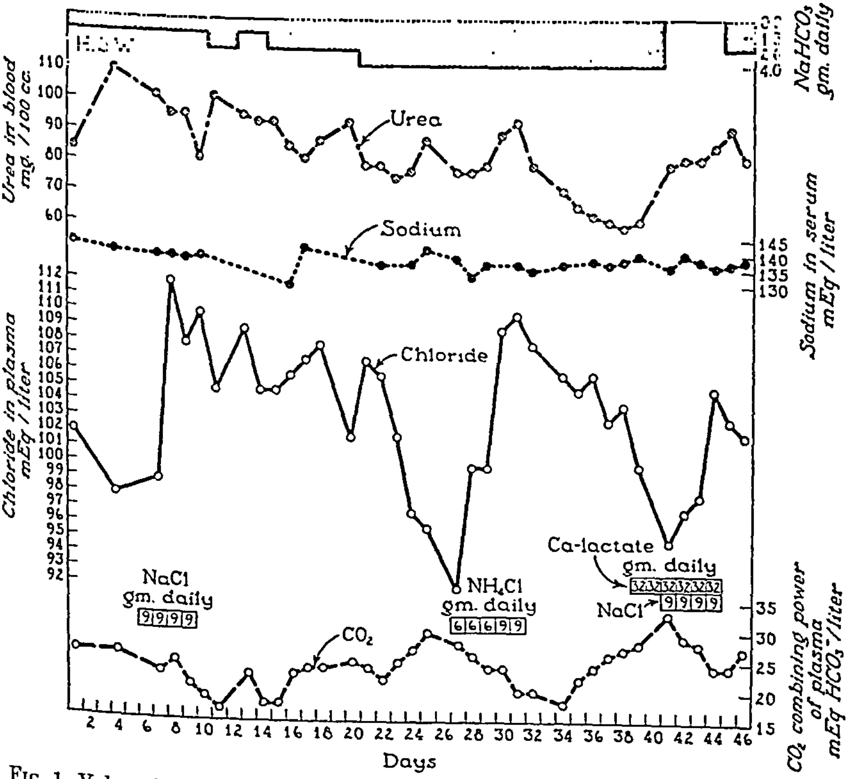

FIG. 1. Values for urea in blood, for sodium in serum and for chloride in plasma.

value for urea in the blood on April 20 was somewhat elevated (84 mg. per 100 cc) (fig. 1), which was thought to be partly on the basis of slowly progressing renal insufficiency and partly due to some degree of dehydration. The values for chloride and bicarbonate in the plasma were entirely within normal limits. His diet was made low in salt (0.5 gm. of sodium) (table 4), and he remained on this diet throughout the period of study. Supplementary sodium bicarbonate was

TABLE 4. *Routine low salt (0.5 gm. sodium) diet**

CONSTITUENTS	AMOUNT
Protein	71 gm
Carbohydrate	201 gm.
Fat	120 gm.
Calories	2,200 gm.
Sodium	0.5 gm.
Chlorine	0.772 gm.
Calcium	0.908 gm
Iron	0.012 gm.

* Diet is adequate in all vitamins according to recommended allowances of the National Research Council.

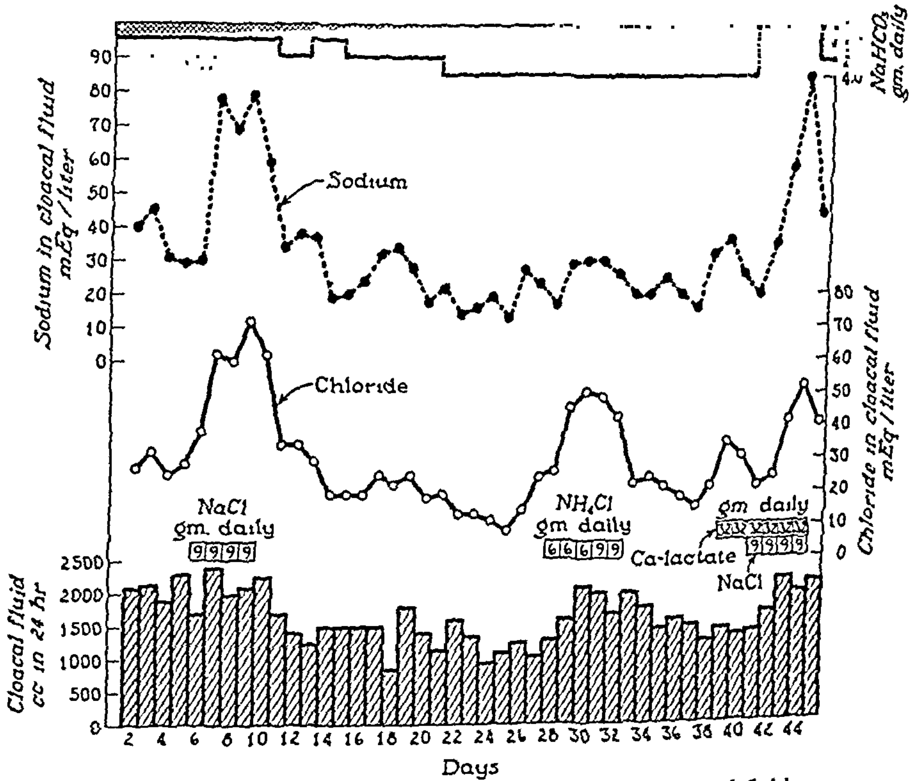

FIG. 2. Values for sodium and chloride excreted in cloacal fluid.

administered in doses indicated in figures 1 and 2. On the sixth day of the study (April 25), the patient was given 9 gm. of sodium chloride daily by mouth. Within 24 hours polydipsia developed with frequency and urgency of "urination." The second day of receiving sodium chloride (seventh day of the study) he reported that he felt weak and tired generally, had stopped perspiring and had lost his appetite. On this day, the value for chloride in the plasma had risen to 111.8 milliequivalents per liter, although the value for carbon dioxide combining power of the plasma still remained within normal limits at 24.8 milliequivalents of bicarbonate per liter. In the 4-day period during which the patient took 9 gm. of sodium chloride daily, his weight dropped from 161 to 153 pounds (73 to 69 kg.).

Within 48 hours after administration of salt was discontinued, the value for plasma chloride had decreased to a level only slightly above normal. The value for carbon dioxide combining power continued to fall to 16.8 milliequivalents of bicarbonate per liter. Despite the fall in plasma chloride level after salt was withdrawn, the patient's symptoms continued unchanged. The dosage of sodium bicarbonate was increased to 2.6 gm. daily. Forty-eight hours later, the patient reported that he was less nervous and tired, that he had slept better the previous night with less frequency and urgency, that polydipsia and the salty taste in his mouth had disappeared, and that his appetite had improved.

During the following 12 days (fourteenth to twenty-sixth day of study), the patient remained free of symptoms. Beginning on May 16, 1949 (twenty-seventh day of study), he was given 6 gm. of ammonium chloride daily by mouth for 3 days. The dosage of ammonium chloride then was increased to 9 gm. daily; the value for plasma chloride rose sharply but there were no subjective symptoms. Twenty-four hours after administration of ammonium chloride had been increased to 9 gm. daily the value for plasma carbon dioxide combining power dropped from 24.4 to 20.1 milliequivalents of bicarbonate per liter, and on this day (May 20, thirty-first day of study), the patient reported that he felt tired, weak, and very drowsy. He also reported a return of frequency and urgency, and was of the opinion that the volume of cloacal fluid passed during the previous twenty-four hours had increased (fig. 2). The administration of ammonium chloride was stopped on May 20, 1949, and within 6 days (May 26) the value for carbon dioxide combining power had returned to normal, although hyperchloremia persisted.

On May 28, 1949 (the thirty-ninth day of study), the patient was placed on a normal diet and was given 32 gm. of calcium lactate daily by mouth, and administration of sodium bicarbonate was discontinued 2 days later. On the fourth day that calcium lactate was administered, the patient again was given sodium chloride in a dose of 9 gm. daily. Within 24 hours after administration of sodium chloride was begun, he noticed some frequency and urgency as well as increase in the volume and fluidity of stools, but otherwise he felt entirely well. On the sixth day of administration of calcium lactate the plasma chloride level had risen to 105.2 milliequivalents per liter, and there was a decrease in the value for the carbon dioxide combining power of the plasma to 23.9 mEq. HCO_3 per liter. On this day, the patient noticed a distinct salty taste in his mouth, without the other symptoms and signs characteristic of hyperchloremia. The following day he resumed a qualitative low chloride diet (table 4), administration of both calcium lactate and sodium chloride was discontinued, and on dismissal he was instructed to take 2.6 gm. of sodium bicarbonate daily.

He has continued this program for about a year and has had no symptoms.

He returned for re-examination once, and on this occasion the electrolyte pattern of his blood was essentially normal.

Only the intelligence and unusual co-operation of the patient whose case we are reporting made this study possible. The patient was meticulous in regard to his diet, medications and collection of specimens, and his reporting of subjective manifestations was regarded by us as accurate.

Although on the basis of recurrent infections of the upper part of the urinary tract in the past 11 years and bilateral renal calculi, the patient undoubtedly has some degree of renal parenchymal damage to account in part for his low-grade renal insufficiency, the fluctuation in urea levels, and the persistently near normal levels for creatinine in the serum lead us to assume that his renal function is essentially adequate and that elevations in the levels of urea and sulfate in the blood may be the result of absorption of these substances from the urine across the rectal mucosa. That his episodes of hyperchloremia have not developed on the basis of decreased excretion of salt by the kidney was shown by the relatively normal concentrations of chloride in the urine recovered from his nephrostomy tube (table 3). We are of the opinion that if we were to institute continual lavage of the lower part of the bowel with tap water for a period of several days, we might be able to "wash out" sufficient urea and sulfate to reduce the levels of these substances in the blood to normal or near normal.

That hyperchloremia may exert a diuretic effect is evident from examination of figure 2. The increased volumes of cloacal fluid during the periods of hyperchloremia coincide closely with the patient's observation of frequency and urgency of "urination" during the periods when he was taking either sodium chloride or ammonium chloride.

The increased concentrations of both sodium and chloride in the cloacal fluid during the period of increased intake of sodium chloride, closely parallel the rise in the level of chloride in the plasma. In the case of chloride, it is impossible to ascertain whether this occurs because an excess amount of ingested chloride is not absorbed initially from the bowel, but is excreted unchanged as sodium chloride, or because urine containing an unusually high concentration of chloride is eliminated before a maximal amount of chloride can be reabsorbed from the urine across the rectal mucosa. Since, from repeated determinations of electrolytes in feces of normal subjects and of patients suffering from conditions other than that under discussion in the present report, it has been noted that sodium usually is found in feces in infinitesimal amounts,[2] we may assume for all practical purposes that the concentrations of sodium in cloacal fluid represents the amounts of that ion excreted by the kidneys. Therefore, one might speculate that the increased concentrations of sodium in cloacal fluid during the period when the patient was taking sodium chloride occurred because an excess amount of ingested sodium was not absorbed from the gastro-intestinal tract but was excreted unchanged as sodium chloride, or because the amount of sodium initially absorbed in excess of that needed to satisfy normal requirements for sodium in serum was excreted by the kidneys and was not reabsorbed from the urine across the rectal mucosa. Acceptance of the latter supposition plus the relatively minor variations in levels of serum sodium during hyperchloremic episodes would lend support to our contention of essentially adequate renal excretory function, at least in so far as the excretion of sodium is concerned, and might further suggest that reabsorption of electrolytes across the rectal mucosa is selective in nature.

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[2] Power, M. H.: Personal communication to the authors.

When the patient was given ammonium chloride, hyperchloremia and acidosis developed (fig. 1), with a corresponding increase in the concentration of chloride in the cloacal fluid, but with only minor increase in the concentrations of sodium. The slight rise in values for sodium in the cloacal fluid we have interpreted as being the result of the diuretic effect of administration of ammonium chloride since administration of ammonium chloride would probably result in excretion of both sodium and potassium in the urine. In our opinion this interpretation lends further support to the theory of normal renal excretion of sodium and raises the possibility of inhibition of sodium reabsorption across the rectal mucosa.

Careful study of the behavior of chloride and bicarbonate levels in the plasma during the periods of induced hyperchloremia and acidosis suggests that hyperchloremia may develop rapidly after the ingestion of significantly large quantities of chloride, and that this situation may antedate the development of acidosis by one or more days. Conversely, it would appear that in correction of the electrolyte imbalance by restriction of salt and supplementation with sodium bicarbonate, values for the carbon dioxide combining power of the plasma may return to normal or near normal levels before the hyperchloremic state is corrected. If the subjective observations of the patient are to be relied on, it would appear that thirst, polydipsia, anhidrosis, polyuria, frequency, urgency, anorexia and a salty taste in the mouth are factors of hyperchloremia, whereas weakness, fatigability, drowsiness and a feeling of malaise or prostration may be associated more with acidosis.

In order to explore the possibility that an attempt to bind chloride to a cation less readily absorbed from the bowel than sodium might result in decreased reabsorption of chloride, the patient was given large doses of calcium lactate by mouth in conjunction with sodium chloride. Hyperchloremia did not occur until the fourth day of ingestion of salt, and then only a moderate rise in plasma chloride was noted. It is interesting to note that in the presence of calcium lactate the ingestion of salt produced a less marked effect on the carbon dioxide combining power of plasma than when salt was given alone.

COMMENT AND SUMMARY

The specific mechanism by which hyperchloremic acidosis develops after bilateral ureterosigmoidostomy still is not clear. In our opinion, however, the present study substantiates the supposition that reabsorption of chloride from urine stored in the rectum and sigmoid is responsible, since hyperchloremia developed after administration of both sodium chloride and ammonium chloride.

Increased excretion of sodium with relatively small fluctuation in levels of serum sodium in the presence of hyperchloremic acidosis suggests to us that excess amounts of sodium are excreted by the kidneys but are not reabsorbed across the rectal mucosa. This would further substantiate a hypothesis that absorption of electrolytes and other substances across the wall of the rectum and sigmoid is selective in nature.

The tardy development of hyperchloremia and absence of clinical manifestations of acidosis from the ingestion of salt in the presence of calcium lactate suggest that this substance may retard absorption of chloride across the rectal mucosa and that either calcium lactate or calcium carbonate might be more suitable "alkalinizing" agents than sodium bicarbonate. Further study, however, is required before this possibility can be proved or disproved.

The results of this study as well as management of other patients who have had hyperchloremic acidosis after bilateral ureterosigmoidostomy offer convincing evidence that this complication can be adequately controlled by giving the patient a diet restricted in sodium chloride, with the supplementary use of sodium bicarbonate, in doses sufficient to effect adequate replacement of bicarbonate without producing alkalosis. As stated in our previous paper, "the degree of salt restriction in the diet and the dosage of sodium bicarbonate cannot be standardized but must be regulated according to the electrolyte response in each patient."[1] If a commercial salt substitute is used, care should be taken that the product does not contain one or more "chloride" salts as ingredients.

Adequate explanation is wanting as to why hyperchloremic acidosis develops early after bilateral ureterosigmoidostomy in some cases whereas in others clinical or laboratory evidence of electrolyte imbalance may not appear for long periods thereafter.

Admittedly, no definite conclusions can be drawn from observations made in the study of one case, but we believe that certain features may be considered of significance in pointing the way to further investigation.

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INFILTRATION TREATMENT OF HUNNER ULCER

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Hunner ulcer is characterized by persistency, pain and dysuria which very frequently limit the life activities of its victim.

Our problem is to increase bladder capacity by decreasing the sensitivity and fixation of Hunner ulcer areas, without adding surgical scar. Etiologic factors and complicating infections add many and diverse diagnostic and therapeutic considerations to each case of Hunner ulcer. To understand varying degrees of success or failure following infiltration treatment requires that we limit our analyses of involved clinical physiology, and pathological changes, as well as clinical manifestations of the disease to the uncomplicated case of Hunner ulcer.

TECHNIQUE

A 20 cc Luer syringe is attached to a 14 inch flexible needle, which may have either a straight or curved detachable point (fig. 1). The curved point is particularly useful for infiltrating a Hunner ulcer located either on the side wall or near the internal orifice of the bladder. In these latter instances the McCarthy cysto-urethroscope should be at hand, otherwise the needle is carried by an operating cystoscope. The 14 inch needles can be purchased from any instrument company. In time, longer flexible shafts will be available from the American Cystoscope Makers, Inc., New York, N. Y., and will be very helpful.

A 20 cc syringe is filled with an aqueous solution of 1 per cent novocain (procaine hydrochloride) containing one drop of adrenalin to the ounce. Of this solution, ½ to 5 cc is injected by an assistant, each time the cystoscopist changes the location or depth of the needle point. The injection is started at the periphery of a Hunner ulcer. It is continued throughout the involved mucosa and submucosa, until the surface blanches to some extent, and then throughout the muscularis, attempting to include either the serosa, or outer fibrous bladder coat when injecting below the peritoneal reflection. We try to actually thicken the area with fluid! Each area is injected from mucosal surface to outer bladder coat. The density of an area of interstitial cystitis often requires that the novocain solution be injected with considerable pressure. At times it is even difficult to drive the needle into the center of the lesion, in which case we are forced to begin our injection at the periphery. As bleeding, though slight, obscures vision, it is well not to fracture the mucosa of a Hunner ulcer by overdistention. The bladder is emptied before the injection is started; to prevent bleeding, we inject a central velvety red ulcer surface last. If a point of injection bleeds upon with-

Read at annual meeting, American Urological Association, Washington, D. C., May 31, 1950.

Previously reported, D. K. Rose: The Male Genito-Urinary System. In *Operative Technic in Specialty Surgery*, edited by Warren H. Cole. New York: Appleton-Century-Crofts, Inc., 1949, pp. 670–718.

drawing the needle in spite of these precautions and the adrenalin, a second injection immediately proximal to the bleeding may stop the ooze by pressure; or pinpoint electrocoagulation may be used. A constantly full bladder (about 80 mm. Hg intracystic pressure) definitely lessens bleeding.

A caudal, low spinal, or general anesthesia is probably necessary in all cases, since as many as 25 to 50 separate punctures, each a 1 to 5 cc injection, may be made into and about each Hunner ulcer. The maintained distention of the bladder would be extremely painful, except possibly in a grade 1 ulcer, without a general anesthetic. We have not found a solitary grade 1 ulcer since we began this work.

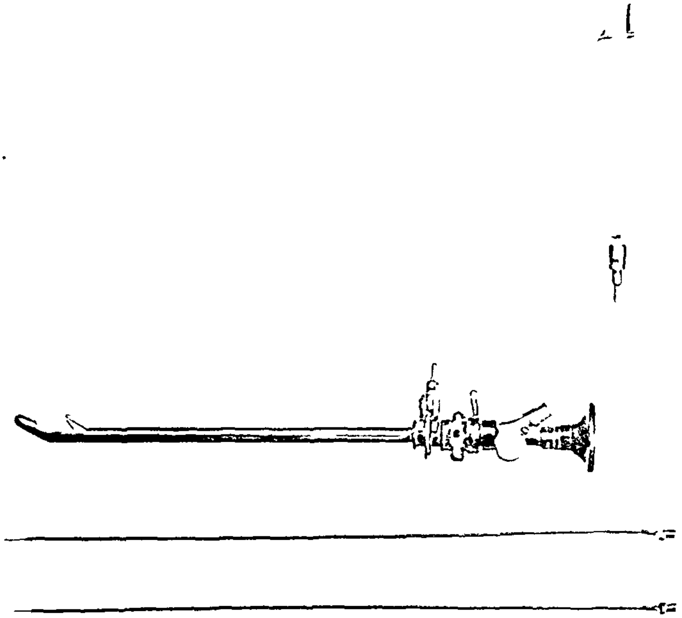

FIGURE 1

CLINICAL PHYSIOLOGY

Pain on overdistention, with frequent voidings of small amounts of urine and definite urgency, occurs with B. coli cystitis as well as with Hunner ulcer. Cystometrograms functionally differentiate these diseases and graph their symptoms, and show that to treat a Hunner ulcer with understanding, we must give full consideration to the entire wall of the bladder, as well as to the lesion itself.

In one case (diagnosis: acute cystitis, B. coli) we have a strongly contracted bladder wall, almost a maintained voiding reflex. The inflamed mucosa will not tolerate weight of urine upon its surface! This means urgent, and frequent voiding; therefore, a decreasing bladder capacity. The cystometrogram is expulsive in type, small capacity with pain and high intracystic pressure, and there is almost immediate effort to void around the catheter (fig. 2).

In another case (diagnosis: Hunner ulcer, urine not infected) the patient complained of urgent and frequent voiding, small bladder capacity, quite similar to the conditions described in the foregoing case. In the second case, although

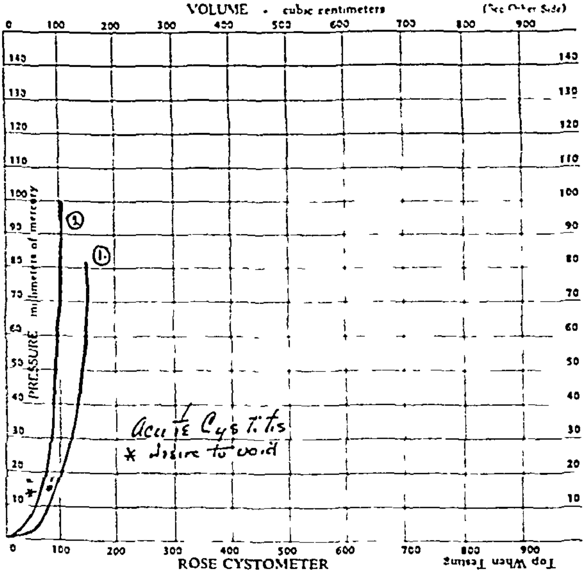

FIGURE 2

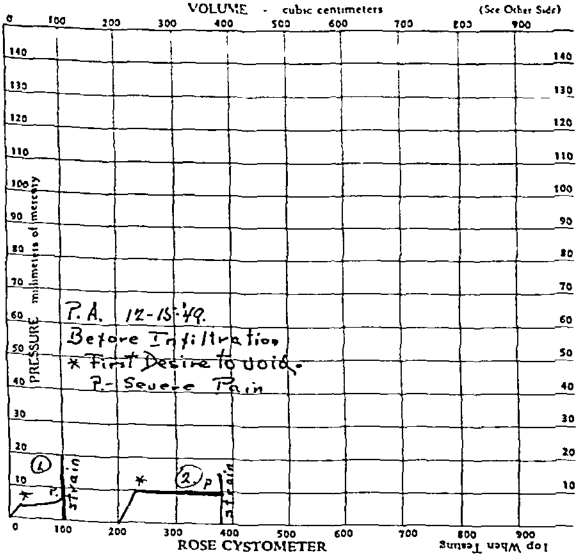

FIGURE 3

filling the bladder is painful, a reflex emptying contraction is definitely inhibited to prevent a painful increase in intracystic pressure. Long inhibition produces bladder contraction. The patient's inhibition is demonstrated cystometrically by the low voluntary and involuntary intracystic pressure lines (fig. 3), associated with severe pain on bladder filling. One is able to inhibit bladder contraction chiefly by voluntarily elevating the anterior perineum and, therefore, the internal bladder orifice. This voluntary movement prevents urine from passing into the urethra, where its presence would stimulate an involuntary bladder contraction. The abdominal muscles and diaphragm play their part in protecting the bladder from any increase in intra-abdominal pressure, by not contracting at such times. Obviously, this patient with an inhibited bladder would not void around the catheter, as did the patient whose cystogram is depicted in figure 2.

Prior to cystometric studies of Hunner ulcer, it was my opinion that the bladder wall became strongly contracted in response to an irritable Hunner ulcer in the same manner as in cases of cystitis. If this were true, we should have a *cystitis type of cystometrogram and we would be unable to stretch the bladder.*

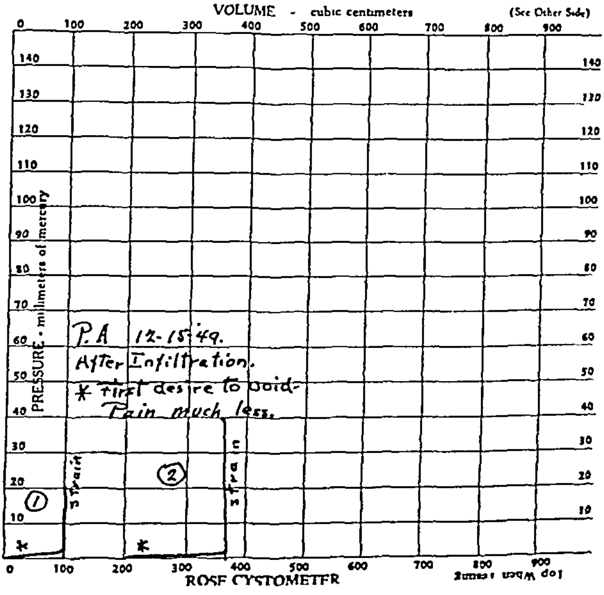

FIGURE 4

Fortunately, an inhibited bladder, a cramped bladder wall can be stretched by repeated hydraulic distention. These facts explain the partial success of therapeutic hydraulic bladder distention, and advise us that our patients should also practice self-distention of their bladder by not voiding until absolutely necessary. These deductions led to the idea that if the Hunner ulcer could be desensitized for a sufficient period of time the inhibited bladder in some cases would return to a near normal capacity.

The cystometrogram depicted in figure 4 was made 24 hours after infiltration of three Hunner ulcers in the patient whose cystometrogram before infiltration is shown in figure 3. We have a residual contraction produced by years of inhibition of the bladder wall. The principal difference between the cystometrogram in figure 3 and the one shown in figure 4 is that the patient can now strain with more force and less pain, although a marked amount of residual bladder contraction remains. The patient is voiding more at a time, 4 to 7⅓ ounces at night, and as infrequently as every 4 to 6 hours. It is not considered wise to repeat cystometrograms after an infiltration treatment, as filling and emptying a bladder stimulate its contraction by stretch reflex; consequently, figure 4 depicts the only postinfiltration cystometrogram made so far.

PATHOLOGY

A microscopic cross section through a fully developed Hunner ulcer shows inflammation of varying degrees. There is an increase in vascularity, definite edema, many white blood cells, chiefly lymphocytes, a few red blood cells, and of prime importance, a large amount of hyperplastic connective tissue, all of which contribute to give the lesion its characteristic hyperemia, thickness, fixation, and decreased elasticity. The severe pain typically increased by bladder wall stretch suggestively is associated with the resultant increased tension within the lesion, where inflammatory changes are found inside the nerve sheaths, in dilated lymph spaces, and lymph channels about the many new and tortuous blood vessels. These structures, together with (motor) parasympathetic ganglia within the Hunner ulcer and entire bladder wall receive "stretch" sensory stimulation with varying amounts of bladder filling, depending upon the degree of bladder contraction. Increased tension within the lesion is explained upon a histopathologic basis by the distribution of new and old hyperplastic connective tissue, found throughout the lesion, but in greatest amounts within the submucosa. The mucosa becomes fixed to the muscularis, and therefore cannot slide smoothly, and painlessly, over the muscle layer when the bladder distends or empties. To loosely connect the mucosa and muscularis is the chief function of the submucosa. It is also because of this pathologic mucosal fixation to the muscularis that we see a mucosa fracture of a Hunner ulcer when the bladder is filled for cystoscopic examination.

Further, in the analysis of pain, hyperplastic connective tissue actually wraps and binds individual muscle bundles, even groups of muscle fibers. This should contribute to the pain of stretch as well as to decreased elasticity. In turn, the muscularis, with similar importance, may be fixed to the thickened, fibrous outer coat of the bladder wall, even to the peritoneum, or deeper pericystic tissue.

EFFECTS OF INFILTRATION

Immediately, we think of the specific anesthetic action of novocain or procaine hydrochloride, and it is true that our immediate relief is almost complete in very nearly all cases, although the bladder capacity does not increase immediately nor proportionately. This specific effect we must consider as temporary; the more prolonged relief we have frequently realized must be due to fluid infiltration, which changes the region of interstitial cystitis (when not previously scarred by cystoscopic diathermy) into a *soft*, almost edematous mass. In 1 case, at cystoscopic examination, 6 weeks after infiltration, the area of Hunner ulcer was still edematous, which should not be due to the infiltration after such time. Therefore, this finding may have been reactionary edema due to the many punc-

TABLE 1

PATIENT	FIRST VISIT TO BARNES HOSPITAL OR OFFICE. HISTORY	GENITO-URINARY DIAGNOSIS. GRADE OF HUNNER ULCER. BLADDER CAPACITY	GYNECOLOGICAL OR OTHER COMPLICATION	THERAPY FOR HUNNER ULCER PRIOR TO INFILTRATION TREATMENT	DATE AND RESULT OF EACH INFILTRATION TREATMENT
			Grade 2		
Mr. P. Age 53.	10-10-49. Frequency and urgency of urination; day to every few minutes, nycturia to 12 times. Pain in bladder, penis and both testes. Suprapubic pain relieved by voiding.	10-13-49. Negative genito-urinary findings except a single grade 2 Hunner ulcer on dome of bladder. Bladder capacity small, not measured.	None. Chest film negative.	None	Oct. 13, 1949. First infiltration treatment. Single ulcer on posterior wall of bladder infiltrated with 20 cc 1% novocain solution. Result: frequency persists, though less, with complete relief from pain. Oct. 17, 1949. Second infiltration treatment. Hunner ulcer infiltrated with 14 cc 1% novocain solution. Greatly relieved. Oct. 20, 1949. Discharged. No pain. Voiding 300 cc at a time. March 1950. Patient reports: "Bladder, comfortable."
Mrs. B. Age 62.	10-9-44. Frequency of urination; "even 30-45 minutes day and 5 to 6 times at night." Pain left groin, hip and leg not relieved by voiding. Postpartum cystitis 40 years ago.	10-9-44. Urine not infected. Grade 2 to 3 confluent Hunner ulcers, left bladder wall. Bladder capacity to pain 130 cc with local anesthetic. Developed a B. coli cystitis 1948, cleared with sulfadiazine. 1949, second Hunner ulcer found on right bladder wall.	Atrophic vaginitis. Urethrocystorectocele, repaired 1948.	For 4 years hydraulic and "self" bladder distention, with instillations of ⅛ to ½% solutions silver nitrate. Maintained average bladder capacity of 250 cc once able to distend bladder to 400 cc. No cystoscopic diathermy.	1) 11-2-48. First infiltration treatment using 50 cc 1 per cent novocain solution. Pentothal sodium anesthesia. Complete relief for 1 month, after which bladder capacity increased to average of about 325 to 350 cc. 2) 11-5-49. Second infiltration treatment with 100 cc 1% novocain, over right and left bladder walls. Pentothal sodium anesthesia. Retention of urine followed, catheterized of 850 cc urine, after which quite severe hematuria. Patient reported Feb. 1950 "well," but returned to office April 5, 1950, with mild symptoms of Hunner ulcer.
Mrs. S. Age 56.	1-9-46. "Terrible bladder pain and frequency of urination," as often as every 20 minutes for past 3 months. First bladder irritation 6 mos. ago.	Urine not infected. 1-9-46. Hunner ulcer grade 2 located on floor of bladder. 1-30-46. Bladder capacity 350 cc with patient under general anesthetic.	Gallbladder disease.	Bladder distention to 350 cc at time of first cystoscopic examination; gave definite relief for 12 days. Later, hydraulic and "self" bladder distention, followed by instillation of ½ or 1% silver nitrate, 50 to 60% relief. Cystoscopic	Sept. 1948. Attempted infiltration, in office, with local anesthesia. Able to inject very little novocain solution into mucosa. Partially relieved for 2 months. 1) 10-16-48. First infiltration treatment with pentothal sodium anesthesia, 15 cc 1% novocain solution injected into ulcer. "Perfectly comfortable" for 3 months.

				diathermy treatment 4-20-49, *did not relieve patient.* B. *coli found in urine, once in* 1948, *disappeared with sulfadiazine.*	2) 6-3-49. Second infiltration treatment. Pentothal sodium anesthesia. 15 cc 1% novocain solution injected. "Well and very grateful" for 9 months. 3) 5-2-50. Third infiltration treatment, with pentothal *sodium anesthesia.* At this time 2 Hunner *ulcers were found.* The older, larger lesion injected with 70 cc, and the more recent and smaller *Hunner* ulcer injected with 10 cc 1% novocain solution. Bladder discomfort persisted for 3 days, *apparently* due to urethral irritation as on the third postoperative day the patient was *completely* relieved of pain and frequency of urination.
		Grade 3			
Miss A. Age 37.	12-2-49. Onset 7 years ago, with *increasing* frequency and urgency *of urination.* Day frequency marked with *nycturia* to 12 times. Suprapubic pain, right side, partially relieved *after emptying* bladder. Upper urinary tract *normal.* Recurrent cystitis, *mixed* infection. Patient extremely apprehensive, moves in *jerks* with least thought of pain.	12-2-49. *Occasional* pus cell, no bacteria in urine. *No residual* urine. Three grade 3 *Hunner ulcers,* located each lateral wall *and dome* of bladder. Considerable scar about each lesion. Voids 2 to 4 *ozs.* at a time.	Chronic trigonitis and urethritis. *Allergic to opiates.* Suspension of uterus 1937. Thyroidectomy 1940.	*Contracted* bladder orifice resected. *Cystoscopic* diathermy twice, and many bladder dilatations, followed by *instillations* of silver nitrate solution, during previous 7 years.	12-13-49. *First infiltration* treatment, pentothal sodium anesthesia, *using* 35 cc 1% *novocain* solution. Result: *Frequency of urination and painful voiding* relieved. *Pain in low abdomen* persists. *Cystometrograms* 1 and 2 (figs. 2 and 3) before and after bladder infiltration, were made with this patient. Result: 1-8-50. Bladder capacity *to* 6 *ozs.* days *and to* 7½ *ozs.* nights. 1-10-50. Capacity 3 *to* 4 *ozs.* 3-7-50. Capacity 4 *to* 5 *ozs.* "I would be very happy about the bladder if I were not having the worst kind of trouble with my nerves. Not as much pain."
Miss O. Age 67.	12-30-49. During day voids small amounts of urine with great urgency. *Nycturia* 8 times. Pain right groin.	12-30-49. *Urine not infected* at first observation became infected after infiltration of *Hunner ulcer.* Cleared with sulfa and antibiotics. *Grade* 3, four Hunner ulcer areas. Bladder capacity 380 cc.	Cysto-urethrocele. Chronic urethritis. Urethral caruncle.	No previous treatment.	12-31-49. First infiltration treatment. Pentothal sodium anesthesia. 10 cc 1% novocain solution *injected* into *two* confluent Hunner ulcers on left dome, and 15 cc 1% novocain solution injected into two confluent Hunner *ulcers on floor of* bladder. Discharged. "Some pain in right groin but no bladder *symptoms.*" Nycturia none as a rule, *occasionally once.*

TABLE 1.—(*Continued*)

PATIENT	FIRST VISIT TO BARNES HOSPITAL OR OFFICE. HISTORY	GENITO-URINARY DIAGNOSIS. GRADE OF HUNNER ULCER. BLADDER CAPACITY	GYNECOLOGICAL OR OTHER COMPLICATION	THERAPY FOR HUNNER ULCER PRIOR TO EACH INFILTRATION TREATMENT	DATE AND RESULT OF EACH INFILTRATION TREATMENT
Grade 3					
Mrs. G. Age 66.	10-4-41. Very frequent urination; to every 5 min. day and night, with severe suprapubic pain. Onset after hysterectomy 6 yrs. ago.	10-4-41. At least 4 confluent grade 3 Hunner ulcers and many scars of previous cystoscopic diathermy treatments. Generalized cystitis present. Bladder capacity 200 cc after local anesthetic, and 450 cc with general anesthetic. No genito-urinary tuberculosis.	Cysto-urethrocele. Large caruncle, and chronic hyperplastic urethritis present. Hysterectomy 6 yrs. ago. Pulmonary tbc. 30 yrs. ago, in sanitarium 10 mos.	Sulfadiazine and antibiotics. Cystoscopic diathermy of hyperplastic urethritis. Instillations of ¼ to 1% silver nitrate solution. 10-4-41. Diathermy. (Cystoscopic) Hunner ulcer. Improved. 1-22-42. Bladder dilatation (spinal anesthetic) to 400 cc Hunner ulcer healed. 11-18-42. Bladder dilated, pentothal sodium anesthesia, to 450 cc. This treatment repeated 2-18-43 and Feb. 1944, with 450 cc capacity.	Sept. 1949. First infiltration treatment, pentothal sodium anesthesia. Ulcer and scar areas (confluent) infiltrated with 40 cc 1% procaine solution, with complete relief from pain for 2 weeks. and with bladder capacity increase. Voiding 200 cc maximum. 12-1-49. Second infiltration treatment, pentothal sodium anesthesia, using 40 cc 1% novocain solution. Complete relief 4 days only. 12-19-49. Third infiltration treatment, pentothal sodium anesthesia. 60 cc 1% novocain solution. Relief complete. Discharged. Ward patient, out of town, and not heard from since.
Mrs. R. Age 52. (Pa- of Dr. J. Cordonnier.)	9-26-49. Frequent and urgent urination in small amount. Onset after pelvic operation, followed by indwelling urethral catheter.	Cystitis, patient has been given aureomycin. No tuberculosis. Grade 3 extensive Hunner ulcers.	Hysterectomy 1937.	June 1949. "On 3 different occasions bladder was stretched under general or spinal anesthetic, and area of interstitial cystitis fulgurated widely." Followed by "alleviation of symptoms for a short time." She "has been advised, on several occasions, to have ureteral transplantation into the sigmoid, or possibly a cordotomy." Above quotations from a letter referring patient to Dr. Cordonnier.	8-26-49. First infiltration treatment. Large ulcer on dome of bladder, numerous hemorrhagic areas over surface of bladder. Pentothal sodium anesthesia. Bladder capacity about 30 cc. Base of ulcer injected with about 30 cc 1% novocain solution, and biopsy removed. 10-4-49. Interior of bladder still shows extensive Hunner ulcer, base of which injected with 2% novocain; ¼% silver nitrate solution instilled. 11-10-49. Hunner ulcer much smaller. Injected base thoroughly. 12-12-49. Hunner ulcer lightly fulgurated and entire base injected with 1% novocain. Result: March 1950, patient "greater relief than with any previous treatment." 5-7-50. Light pains, but doubtful whether

Mrs. W. *Age 40.*	1-25-49. *Day frequency to every 10 minutes. Severe bladder pressure pain before and after voiding. Nycturia to every 15 min.* Postpartum *cystitis 21 yrs. ago.* Recurrent attacks since.	1-25-49. *Few WBC, no bacteria in urine. 10 cc residual* urine. 1-25-49. Four grade 3 confluent *Hunner ulcers* involving *right* wall, dome and *left wall* of bladder. Bladder capacity 200 cc. after local anesthetic. At least one half of bladder surface involved with scar or Hunner ulcers.	Urethrocystoureterole present. Gall-bladder *disease.*	*For past 4 yrs. (since 1940) "has had electric needles several times and bladder stretched, under an anesthetic, many times." Cystectomy has been advised.* From 1943 to 1948 bladder capacity *maintained* near 300 cc with two cystoscopic diathermy treatments and repeated hydraulic and "*self*" bladder distentions, and instillations *of ½* to 1% silver nitrate *solution.* 1948. Staphylococci found in urine, cleared with sulfadiazine.	1-25-49. Barnes Hospital, pentothal sodium anesthetic. Bladder almost totally involved with scar and bleeding Hunner ulcers. Could infiltrate with only 12 cc 2% solution of novocain because *of severe* bleeding. No relief. 1-29-49. *Injected* 95% alcohol into submucosa (Alexander) at several *areas.* No relief. 2-10-49. Incised bands between Hunner ulcer (Seaman) with some relief from pain but no decrease in frequency of urination. At *this* time slough of alcohol injection gone. Patient sent home for "*self*" distention of bladder, and instill silver nitrate solution. Pain relieved, but bladder capacity has not increased. 5-16-50. Infiltration, pentothal sodium anesthesia. 3 large areas of confluent Hunner ulcers. Bladder capacity 120 cc under general anesthetic. *Areas* injected with 60 cc 1% novocain solution. 5-18-50. Pain and frequency. Re-injected, under penthotal sodium, with 130 cc 1% novocain solution and 10 cc 1% nupercaine in 1% almond oil. 5-22-50. Pain slightly better, capacity not improved.

tures by the infiltrating needle. There is an open suggestion in my mind, that possibly the repeated punctures alone might have something to do with our results. This is, of course, purely theoretical. In our post-infiltration spongy areas, blood vessels, lymph spaces and channels should be unblocked, and the flow of blood and lymph facilitated. T. O. Powell suggests that lymph stasis may form a favorable medium for the formation of connective tissue. The area has been irrigated! Pressure upon nerve endings and parasympathetic ganglia is less in this edematous tissue, even when the bladder is distended. The submucosa has been thoroughly infiltrated, thereby at least temporarily, freeing it from its painful fixation to the muscularis. Fibrous tissue bands binding divisions of, as well as entire muscle bundles are thoroughly softened by infiltration. The muscularis now should have freer movement and improved circulation. Hopefully the serosa or outer fibrous coat receives similar treatment and effect.

If the patient has been previously treated by cystoscopic diathermy for actual destruction of the lesion, the resulting scar tissue definitely obstructs thorough infiltration, consequently relief may be less satisfactory. Scar tissue bands radiating out from the lesion in some instances may be cut with a fine wire electrode, as J. A. Seaman advises.

REPEAT INFILTRATIONS

When and if pain due to Hunner ulcer returns, days, weeks, or months after the first or subsequent infiltration, we may find the cause in the degree of involvement, a new lesion and its location near the trigone for example, or complicating scar tissue due to previous cystoscopic diathermy or fulguration. More commonly, we find that a longer time is required for resolution of the inhibited bladder wall. Infections, either gynecological or urinary, require treatment, and often are of etiological importance. Eight cases are reported (table 1).

The grading follows that of Dr. John R. Hand, whom I quote:

"Grade 1 represents minimal bladder involvement. On distention there were small, discrete, submucosal hemorrhages, showing variations in form. Occurring chiefly in the trigone and base, however, the lesions caused little or no restriction to bladder capacity."

"Grade 2 represents a more advanced stage of the disease. The lesions were larger, and they gave the impression of a localized edema of the bladder walls. On distention bleeding points could be seen in the thinned out mucosa overlying the edematous areas. The most frequent sites of involvement were the walls. Bladder capacity was considerably diminished."

"Grade 3 represents the most advanced stage of the disease. In the greatest number of cases the lesions were recorded as being "diffuse." The mucosal surface was pale and often showed linear scars of old lesions. While there was bleeding on distention, the dominant finding was a zigzag fissuring which suggested a split along the lines of the underlying vascular network and muscle bundles. Bladder capacity was greatly diminished, being 150 cc or less."

The grade 2 lesion can be accurately outlined, and, therefore, accurately and thoroughly infiltrated. When a grade 3 lesion radiates out from scarred areas to blend with a nearby similar lesion, it cannot be accurately outlined nor infiltrated.

Note that bladder and referred pain may be completely relieved, while frequency of urination may persist, or the opposite may occur. It is hoped that earlier infiltration of a grade 1 lesion will improve our results; until then or until a better infiltrate is found, bladder distention will increase capacity; silver nitrate instillations will decrease mucosal infections; and cutting radiating bands, as suggested by Dr. J. A. Seaman, will favorably supplement infiltration treatment. Our experience with this method of treatment suggests that destruction by diathermy of an entire Hunner ulcer area is not desirable in many, if not all, cases.

I have used the principle of infiltration very successfully once in a case with an extensive post-radiation fibrosis on the floor of the bladder, following treatment with radium for carcinoma of the cervix. A large syringe with a heavy needle was used to infiltrate the scar area directly by way of the vaginal wall. The patient was receiving antibiotics when the injection was made with 100 cc 1 per cent novocain solution. Now, 4 months later, the patient still is relieved of her severe dysuria. Suggestively she too had an inhibited bladder with secondary contraction.

POSTINFILTRATION TREATMENT

Self-distention of the bladder is a valuable postinfiltration treatment. At least once a day direct the patient to drink water freely for an hour or two, and retain urine to tolerance; measure and record the amount voided. This must be accomplished during a period of leisure. The bladder fills to its largest capacity with the patient lying down, head elevated and a pillow under the knees. A bladder capacity record not only serves the urologist with an index of recovery, but the self-distention actually increases bladder capacity. In addition to this we must continue treatment of every possible etiologic factor, particularly infection. Catheterization should be omitted when possible, as its direct effect upon the bladder and its effect reflexly from the urethra, is to decrease bladder capacity; nevertheless instillations of silver nitrate solutions are advisable when trigonitis or urethritis is present. Frequent methylene blue stain or culture of urine sediment must be made to recognize and treat recurrent cystitis.

SUMMARY

Through a long, flexible needle, carried by an operating cystoscope or McCarthy cysto-urethroscope, Hunner ulcers are thoroughly infiltrated with 1 per cent procaine hydrochloride solution, adding one drop of adrenalin to the ounce. The immediate relief is marked. Many months of relief may be realized. The basis of relief, by physiological analysis, is that while the anesthetic action of the solution, per se, is temporary, the effects of fluid infiltration are all important, in that it changes the physical characteristics of the Hunner ulcer. Tension within the area, its fixation, and stasis of lymph are favorably altered. The end result of infiltration should be a thickened, semi-edematous mass, replacing the former hard, fixed area of interstitial cystitis.

Cystometric studies show that the small bladder capacity occurring with a Hunner ulcer is due to a protective inhibition, and not due to the forcefully contracted bladder which occurs with acute cystitis, even though the symptoms may be quite similar. The inhibited bladder can be distended, in time, after the physical characteristics of the Hunner ulcer are changed by fluid infiltration.

Early relief from pain obtained by this method is more frequent than with previous methods of treatment, though repeat infiltrations may be necessary. Bladder capacity does not necessarily increase proportionately to the relief from pain; it is a variable factor. Cases with multiple Hunner ulcers, badly scarred by previous cystoscopic diathermy, do not infiltrate satisfactorily in all instances. Pentothal sodium or caudal anesthesia has been necessary for satisfactory infiltration. Possibly a grade 1 ulcer could be infiltrated with local anesthesia. One infiltration treatment has been helpful in 1 case of bladder scarring following the postoperative use of radium for carcinoma of the cervix.

An infiltrate of possibly either a gel, oil, suspension, or a plastic medium insuring slower absorption of the anesthetic agent, and having the necessary physical qualities, may materially decrease pain and increase bladder capacity. We shall work in this direction.

Finally, I consider infiltration treatment not a cure except rarely, but a method to be added to our present therapy for Hunner ulcer.

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REFERENCES

Adams, A. W.: Proc. Roy. Soc. Med., 35: 434, 1942.
Alexander, J. C.: Dallas M. J., 22: 100, 1936.
Barnes, R. W.: Calif. Med., 66: 347, 1947.
Cristol, D. S., Greene, L. F. and Thompson, G. J.: J. A. M. A., 126: 825, 1944.
Dodson, A. I.: Virginia M. Monthly, 53: 305–10, 1926.
Emmett, J. L.: Proc. Staff Meet., Mayo Clin., 17: 261–263, 1942.
Engel, W. J.: Cleveland Clin. Quart., 6: 307, 1939.
Folsom, A. I. and O'Brien, H. A.: J. Urol., 37: 808–814, 1937.
Hand, J. R.; J. Urol., 61: 291, 1949.
Herbst, R. H., Baumbrucker, G. O. and German, K. L.: Am. J. Surg., 38: 152–167, 1937.
Higgins, C. C.: Ann. Int. Med., 15: 708, 1941.
Hinman, F.: The Principles and Practice of Urology. Philadelphia and London: W. B. Saunders Co., 1935, pp. 912–995.
Howard, T. L.: J. Urol., 51: 526, 1944.
Hunner, G. L.: Boston Med. & Surg. J., 172: 660, 1915.
Hunner, G. L.: Am. J. Obst., 78: 374, 1918.
Kretschmer, H. L.: J. Urol., 42: 385, 1939.
Langworthy, O. R. and Hesser, F. H.: Bull. Johns Hopkins Hosp., 67: 196, 1940.
Meads, A. M.: Urol. & Cutan. Rev., 38: 631, 1934.
Meisser, J. G., and Bumpus, H. C., Jr.: J. Urol., 6: 285, 1921.
Moore, T. D.: J. Tenn. Med. A., 22: 82, 1929.
Nelson, O. A., and Pinard, C. J., Jr.: Northwest Med., 42: 230–233, 1941.
Nesbit, R. M.: J. Urol., 57: 741, 1947.
Ormond, J. K.: J. Urol., 33: 576–582, 1935.
Pool, T. L. and Rives, H. F.: J. Urol., 51: 520, 1944.
Pool, T. L.: Med. Clin. North Amer., 28: 1008, 1944.
Powell, T. O.: Surg., Gynec. & Obst., 78: 605–609, 1944.
Powell, T. O.: J. Urol., 53: 823, 1945.
Quinby, W. C.: Tr. Am. A. Genito-Urin. Surg., 24: 355–361, 1931.
Rose, D. K.: J. Urol., 57: 579–598, 1947.
Rusche, C. and Hager, B. H.: Trans. Am. Assoc. Genito-Urin. Surg., 32: 203, 1939.
Seaman, J. A.: South Med. J., 38: 398, 1945.
Vose, S. N. and Dixey, G. M.: J. Urol., 59: 580, 1948.
Winsbury-White, H. P.: Brit. J. Urol., 5: 249, 1933.
Young, H. H.: Miss. Vall. M. J., 65: 15–19, 36, 1943.
Young, J. R., Jr.: Cleveland Clin. Quart., 2: 51–55, 1935.

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ALPHA-TOCOPHEROL IN TREATMENT OF INTERSTITIAL CYSTITIS: PRELIMINARY REPORT

R. E. VAN DUZEN AND (BY INVITATION) RHOADS MUSTAIN

The treatment of interstitial cystitis or elusive ulcer, as described by Hunner in 1914, has been a problem in our hands through the years. It is probable we have tried all the simpler methods from the various oils, injections, to various medications by mouth especially the estrogens and the sulfa preparations, with indifferent results. Many years ago John Caulk expressed his views by saying that any of the methods would help the occasional case, but none helped every case and that has been our experience. In 1948, we began to treat Peyronie's disease with alpha-tocopherol after the suggestion of Dr. W. W. Scott. We were very much pleased with the results in several cases, and about 6 months later it occurred to us that the same drug might help cases of interstitial cystitis. Both of these conditions run an analagous course. In both instances the lack of contractile and expansile power of the structure involved produces the pain or the deformity. In Peyronie's disease the lesion involves the fibrous sheath of the corpus cavernosum and because the adjacent area cannot be expanded as the remaining corpora, the curvature of the penis results. In the bladder the area of interstitial cystitis is rigid and when one attempts to dilate the bladder beyond a certain point, it is in the area involved that one sees the minute hemorrhages. From this the idea sprang that it was possible that the vitamin E derivative might be of benefit. We have tried the drug on several cases but there are only 6 that we have been able to follow satisfactorily. As in Peyronie's disease, it took about 3 to 4 weeks before any appreciable improvement was apparent. Following this we began to notice that these patients were able to go longer between voiding, that there was less pain on distention, and that the capacity of the bladder gradually increased. In most of the cases we continued to use hydraulic distention of the bladder at intervals of 3 to 4 weeks, and in 1 case the patient now retains 16 ounces of fluid without appreciable discomfort. In 2 cases we have re-examined the bladder at a month and 2 month intervals and the contracted puckered area with the tell-tale blood vessel still remains. However, on distention we did not see the hemorrhage that was seen in earlier observations. This of course is not conclusive because these lesions often come and go and one should not be especially encouraged by the disappearance of the lesion which has previously been observed. These patients have been more comfortable, they are now able to go longer between voidings and they do not have the excruciating pain that they experienced before starting the drug. One patient had had silver nitrate instillations for a long time, repeated fulguration through the cystoscope and various medications, without any permanent results. She was sent to me with the information that her funds were extremely limited, that she lived some distance from us and could we give any treatment which she could carry out at home, otherwise it would be impossible

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for her to take treatments. This patient was given alpha-tocopherol to be taken at home and she has received no local treatments in the past 8 months. After about 4 or 5 months she decided to stop the alpha-tocopherol. Within 2 weeks her symptoms were as severe as before starting the drug. Treatment was again instituted and within 3 days the symptoms were completely relieved and have remained so. In another case similar results were obtained. In the other cases we have been able to observe the patients in the office and have been very well pleased with the fact that they do not have the intolerable pain on distention, especially on over-distention of the bladder and they do not have the painful bladder at night. They are able to sleep. The outlook on life is much better. We have never been sure what the continued use of silver nitrate instillations in the bladder would cause. We have seen cases of argyrosis from argyrol and have seen the pigmentation from long standing treatment with weak solu-

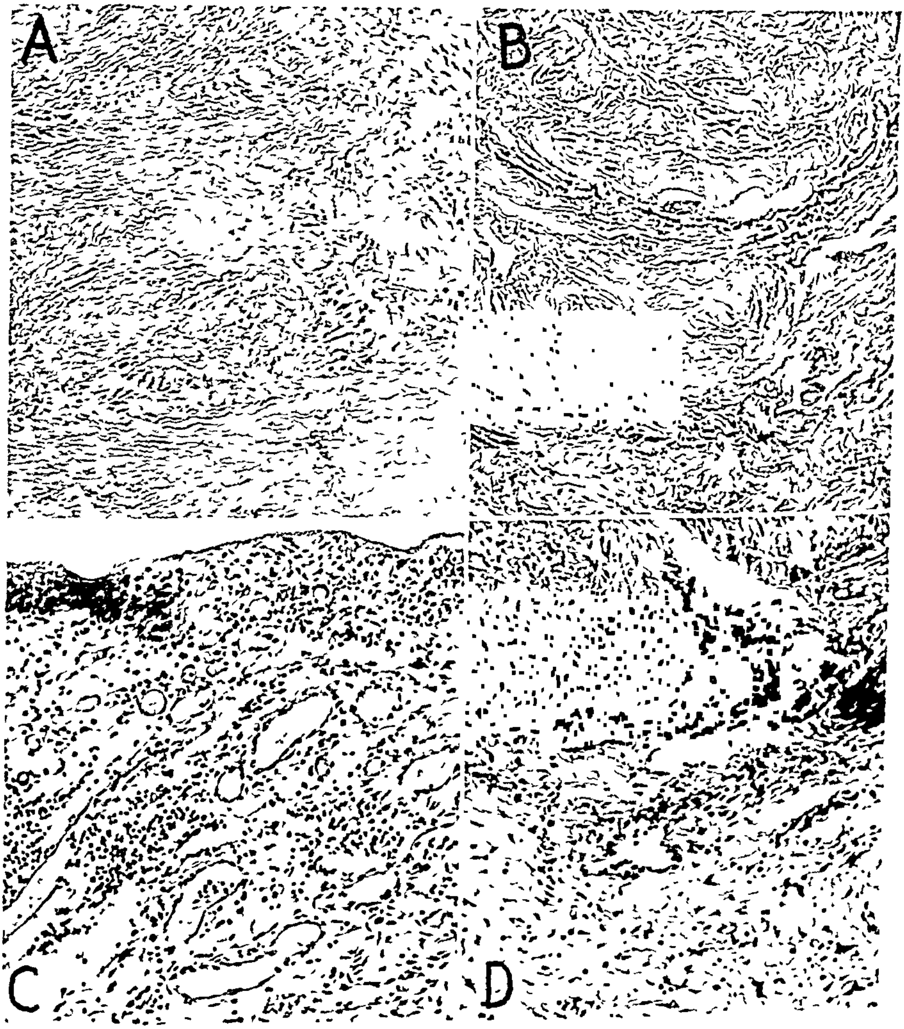

Fig. 1

tions of silver. With the cases that we have tried to treat by the use of silver nitrate and nupercaine solution, as outlined by Dr. Howze some years ago, we have been like the man with the proverbial bear, "we *have not been able to* let go." Our short series has impressed us that we may be able to help these cases by a simple method. These cases were given 300 mg. alpha-tocopherol daily. After 1 month the dosage may be reduced to 100 mg. daily, which is apparently the maintenance dose.

We then attempted to see whether there was any similarity between the lesion of Peyronie's disease, Dupuytren's contracture and interstitial cystitis. Dr. Scott pointed out that the cases with Peyronie's disease and Dupuytren's contracture responded better to the use of alpha-tocopherol than the Peyronie's disease without concomitant Dupuytren's contracture. When we attempted to obtain specimens from these lesions we found that there was not an abundance of material to work with. The cases of interstitial cystitis consisted mainly of biopsy specimens which were not very suitable for study. We did not find a marked abundance of specimens of Peyronie's disease. Dr. Gill of the Southwest Medical School has assisted us in this study and it is his belief that Dupuytren's contracture and desmoid tumors show a great similarity and resemble malignant disease in some respect. There are however, wavy fibrous structures which are supposed to be contractile fibrils, and which are similar to those seen in the plaques of Peyronie's disease. See figure 1. Beyond this similarity he sees no resemblance. It is his impression that Peyronie's disease resembles a scar and it is mainly the fibrous tissue response that is seen. In one plaque new bone formation was noted. Lastly, in cases of interstitial cystitis the scar is not as marked as is the evidence of infection as shown by the many lymphocytes seen, especially in the periphery of the lesion. From this study we do not see a similarity which would suggest that the alpha-tocopherol attacks certain pathological responses. At first it was suggested to us that these lesions were result of collagen dysfunction, however Dr. Gill does not believe that this is true. Our only grounds for advocating the use of the drug is the similarity of response in these different lesions. They all have responded at about the same rate. It is true that in Dupuytren's contracture and in most cases of Peyronie's disease, pain is not the prominent symptom, but there is a lack of power of expansion and contraction in all the lesions and the improvement corresponds to the return of these powers. Two patients who took alpha-tocopherol noticed pelvic congestion and fullness of breasts. They stated the symptoms were similar to those experienced prior to menstruation during their menstrual life. It is possible this estrogenic-like action plays a part in the improvement of symptoms.

CONCLUSION

Alpha-tocopherol, 300 mg. daily by mouth, has improved the symptoms of patients suffering from interstitial cystitis.

The drug does not require repeated office treatments, although we usually dilate the bladder each month.

The drug is relatively inexpensive.

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DISCUSSION

DR. JOHN R. HAND (Portland, Ore.): The papers by Doctor Rose and Doctor Van Duzen pose a provocative question: What happens when multiple action drugs, such as novocain and vitamin E, are used to treat such a disease as interstitial cystitis which is of unknown etiology (apparently caused by many factors) and which affects an organ whose neurophysiology is not understood?

Doctor Rose, with his novocain injections, aims to increase bladder capacity by decreasing the sensitivity and fixation of Hunner ulcer areas without adding surgical scar. In his opinion the basis of the relief he has been able to give his patients is the anesthetic action of the injection solution and, as he says, more important the changes which the fluid infiltration produces in the characteristics of the Hunner ulcer. As Doctor Rose explains, "tension within the Hunner ulcer, its fixation, and stasis of lymph and blood within the lesion are relieved."

It seems to me that in addition to the local effects of anesthesia, muscle relaxation, and vasodilatation a more significant effect of the novocain injection is interruption of a vicious cycle maintained by the reflex arc. The sequence is probably as follows: Nerves coursing through the inflamed areas of the bladder often have damaged sheaths and frayed, exposed nerve endings. When these nerve endings are further irritated by contact with the urine or distention of the bladder, myriad visceral afferent impulses initiated by the irritation are sent to the cord. As these impulses enter the cord, and possibly spill over to higher levels, they produce hyperirritability in the cord, or a so-called local excitatory state. In response to this bombardment, the visceral efferent impulses maintain excessive spasticity of the musculature and blood vessels in the involved bladder area. The result is a continuation of the irritative process in the bladder.

Novocain injected into the Hunner ulcer areas blocks this whirlpool of impulses and thus allows the hyperirritability in the cord to subside. It is conceivable, therefore, that injections repeated at frequent intervals would ultimately break the pattern established by the reflex arc and permit the inflammation in the bladder to subside.

If these assumptions are correct, the treatment carried out by Dr. Rose lends support to my contention that the nervous system plays an important role in the initiation and continuation of interstitial cystitis.

The treatment reported by Doctor Van Duzen attacks the problem of interstitial cystitis from another point of view—that of fibrosis. Doctor Van Duzen has observed that the bladder wall regains expansile power after the use of alphatocopherol. He attributes this to the fact that vitamin E softens or promotes resorption of scar tissue. Hence, he proposes that vitamin E deficiency be given consideration as a cause of interstitial cystitis.

Work on vitamin E has been carried on for 25 years or more. Its earliest clinical use was for gynecologic and endocrine dysfunctions. More recently emphasis has been given to its vasodilating effect and its importance in the nutrition of connective tissue as well as oxidation and metabolism of muscles. Fibrosis is said to be prevented when normal muscle nutrition is maintained. Reports of the efficacy of vitamin E in the treatment of fibrositis, Peyronie's disease, and Dupuytren's contracture lend credence to Dr. Van Duzen's thesis.

It is of interest, also, that the conditions which vitamin E is thought to improve are associated with collagen diseases. Fister considered interstitial cystitis to be a collagen disease. Recent experimental studies indicate that the collagen diseases are associated with a disturbance in hyaluronic acid which is polymerized with protein to form the viscous substance cementing the cells together. It is thought this substance is broken down by the enzyme hyaluronidase and that cortisone may inhibit the destructive action of hyaluronidase. In view of these observations, cortizone may prove to be an effective therapeutic measure for interstitial cystitis.

I enjoyed hearing these two papers, and believe the treatment each described merits trial. In conclusion I should like to emphasize that treatment of the local bladder condition must be supplemented with supportive general measures.

DR. LAWRENCE R. WHARTON (Baltimore, Md.): My experience with alpha-tocopherol in interstitial cystitis has been limited but, such as it is, I am willing to give it to you. I have had only 2 cases in which I have used it. The first patient was a woman who had had interstitial cystitis for a good many years and I had treated her myself for about 9 months without any benefit whatever. After a year or so, she got along pretty well and about two or three months ago, I gave her alpha-tocopherol. She has since then been very much better, but in the meanwhile she has also received urological care.

For two reasons, I think this particular case should be thrown out of consideration because, in the first place, she had the same favorable reaction once before on the same treatment without alpha-tocopherol: and then in the second place, since using alpha-tocopherol, she has also had cystoscopic treatment. The benefit, therefore, is not clear.

In the second case, the patient was one of a group of women who had been receiving alpha-tocopherol treatment for menopausal symptoms. These experiments were conducted by one of our staff at Baltimore. This woman has been under treatment for her menopausal symptoms with the usual dose of alpha-tocopherol for a good many months, and neither the menopausal symptoms nor the urinary tract symptoms have shown the slightest relief.

I would say that these two cases are inconclusive, of course. I would not mention them except that I am on this program and believe that I should. However, I believe as further experience goes along, we will be able to get a better view of the thing.

Since this seems to be an "experience" meeting, I would like to recite a wrinkle I have been using in the treatment of chronic interstitial cystitis in the last year and a half.

(Slide) In interstitial cystitis, the lesion is in the vertex and I hope you will pardon me for showing a picture of a patient in the knee-chest position and the Kelly cystoscope. When the patient with interstitial cystitis lies on her back, then the vertex is high up and this is a very difficult condition to treat. About a year and a half ago, it occurred to me if we turned the patient over and put her in the knee-chest position, then the vertex became the bottom of the cup and any medicine you put into the bladder under those circumstances would immediatly hit the spot and stay there until the patient moved.

With this in view, I had a patient with chronic interstitial cystitis put in the knee-chest position and, by means of the Kelly cystoscope, visualized the ulcer in the vertex and then, using an ordinary medicine dropper, dropped into the Kelly cystoscope and directly onto this ulcer the medicine I wished to apply. I usually start with a weak solution of silver nitrate, 3, then 5, and eventually 10 per cent silver nitrate directly on the ulcer, using perhaps 20 cc, and keeping the patient in this position for a minute or a minute and a half. At the end of that time, we aspirate the bladder completely and remove all of this fluid, and then you can see that the vertex, that has been filled with the silver nitrate, is like chalk; the whole thing has been cauterized and the ulcer has disappeared. I then wash out the bladder and let the patient go home.

I used this last year in 1 case and the result was very good. I gave the patient 3 treatments. Having been treated without any benefit at all for about a year, after about two treatments of this sort, some one month apart, this patient got along for six or eight months without any symptoms whatever. I say that without exaggeration; she had no pain, no symptoms. The symptoms recurred last fall and this spring I have used it in another instance, with about the same result.

That, again, is only two cases; anyhow, these two patients are very much better than they were.

Dr. James A. Seaman* (Springfield, Mass.): I am very curious about these papers, particularly since they are presented by men whom I believe do a lot of substantial thinking urologically. I am thinking constantly of the basic pathology of the so-called ulcer. I rarely see what is really an ulcer. I am thinking always in terms of fibrosis which extends from the mucosa down to and on into the muscularis in various planes perpendicularly, diagonally, horizontally, and a whole hodge-podge pattern.

I am thinking of some way to get rid of this scar tissue which may extend in one little portion of the bladder; it may extend throughout the entire bladder, much like the wire you see in nonbreakable glass, impregnated in the glass. My picture of interstitial cystitis is that, not a superficial ulceration, such as an indolent ulcer of the skin that I can distinctly make out and describe.

The scar tissue is such a hodge-podge that I am wondering how we can dissolve that without dissolving the patient. I think it can be done, but the patient must be preserved. I am not sure it is with infiltration with an anesthetic. I think it will give relief. The edema certainly will relieve the pain symptoms. How long it will give relief, I do not know. I wish Dr. Rose would tell us just how often he does this, and for how long a period he gets relief from these infiltrations.

Four ounces seems a lot of fluid to inject into the mucosa. I do not know whether I would be technically skillful enough to inject this into the bladder I am thinking of, where the fibrous tissue extends throughout the bladder wall. I do not know whether I could adequately get at the anterior portion of the bladder, which is a very difficult place to get at, even to fulgurate.

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* Deceased.

I still believe, as long as the pathological process is one that extends with irregularity, making bands that become shorter and longer, extending throughout the bladder submucosa, you have to do something to cut these bands, and I think if you use the finessing current, the most delicate current you can apply with a fine needle point electrode just touching them so that they give as the bladder distends and the water rushes in, you get a longer relief. I am sure some of these patients that I have treated have had better relief, without any symptoms whatever, and not requiring that it be done again every six months or every nine months.

I am sure I would prefer that to this persistent injection method which is going to give them relief temporarily but not cure the fundamental, basic disease which I think is still going to be there when Doctor Rose finishes his last injection. I wish he would tell us more about that.

DR. D. K. ROSE (St. Louis, Mo.): I am sure that Doctor Seaman's method will be used, and I am certain that I shall continue to use it. It had its greatest advantage when there were bands of scar tissue extending out from Hunner ulcers. Our infiltration is not into the mucosa alone, but throughout the entire thickness of the bladder wall. Dr. J. C. Alexander, some years ago, infiltrated the mucosa alone with alcohol. I repeated his work and found that it resulted in necrosis of the mucosa and submucosa. We start our infiltration far out from the Hunner ulcer, and continue in to the lesion itself. I think if Doctor Seaman would do this he might be surprised to see how the finer bands of a Hunner ulcer disappear with infiltration. However, I think the heavier bands should be cut after his method. The longest time the cure has continued so far is 7 months. We have 1 case of complete failure. This woman had had cystoscopic diathermy 10 or 12 times. Her bladder was a mass of scar tissue. We cut bands in this case, with possibly an immediate increase of an ounce in her capacity.

The relief of pain is instant, and continued relief is due to thorough infiltration, change in the physical characteristics of the ulcer area.

We made a cystoscopic examination in 1 patient 6 weeks after infiltration, and found that the local edema was greater than immediately after the infiltration.

Our postoperative treatment includes self-distention, and possibly in a few instances hydraulic distention, also silver nitrate instillation. However, I am of the opinion that infiltration treatment should supercede electrocoagulation or diathermy of the ulcers, as we do not leave scar tissue. In general, our results are very gratifying, particularly in those ulcers classified grade 2, after Doctor Hand's method of grading.

DR. REX E. VAN DUZEN (Dallas, Texas): I did not present this to you as a final report. I do not believe it is the last word. I think anything that we can do to stimulate thought and help these miserable patients is worth while. I have always been interested in the recital of the case history of a patient who tells you that the only time in her life that she has been comfortable was during pregnancy. I think there must be some connection between the estrogens and the relief that comes at that time.

I think we must be very careful when we give alpha-tocopherol not to continue with too large a dose. I think as soon as the symptoms are ameliorated, you should cut down to a maintenance dose, which apparently is about 100 mg. daily.

In an occasional case in which I have not had the results I thought I should have, I have combined it with sulfanilic acid, in which we use ½ teaspoon of sulfanilic acid, ½ teaspoon of soda-bicarbonate, and ½ glass of water, 3 times a day. That helps to soften tissue.

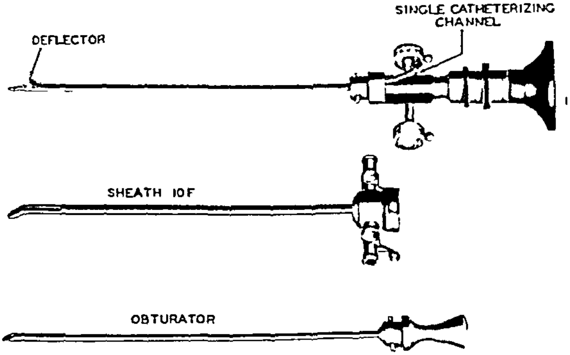


FIG. 1. McCarthy infant cystoscope with telescope, single catheterizing channel and deflector. Sheath is 10F and an obturator is provided

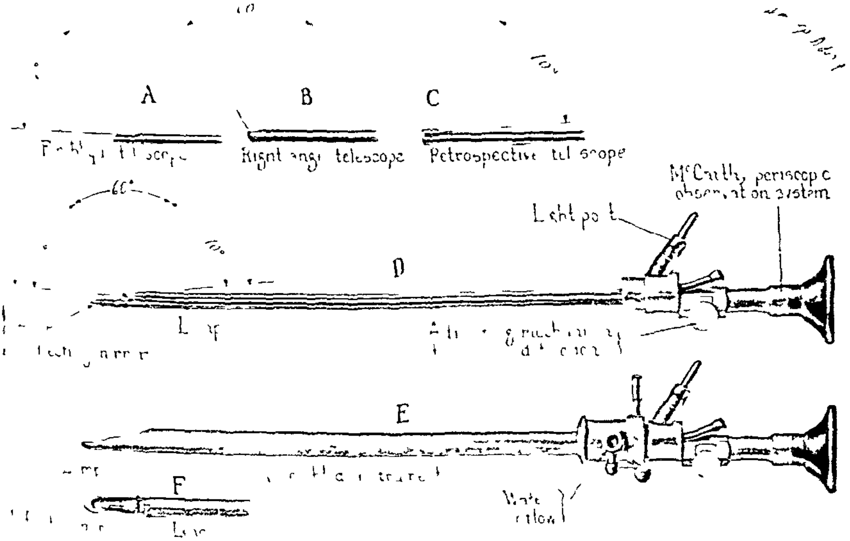


FIG 2 McCarthy foroblique retrospective panendoscope Illustration demonstrates visual field and component parts of instrument

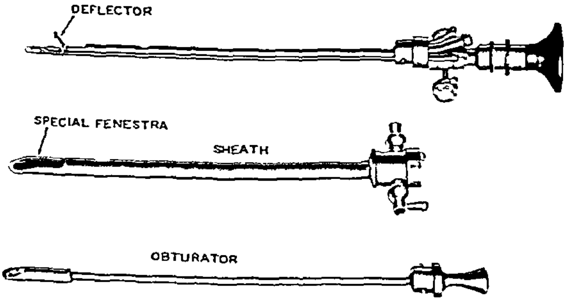
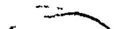


FIG 3 McCarthy deflecting panendoscope with component parts



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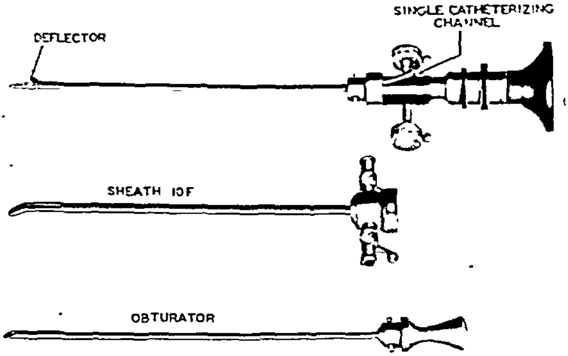

FIG. 1. McCarthy infant cystoscope with telescope, single catheterizing channel and deflector. Sheath is 10F and an obturator is provided.

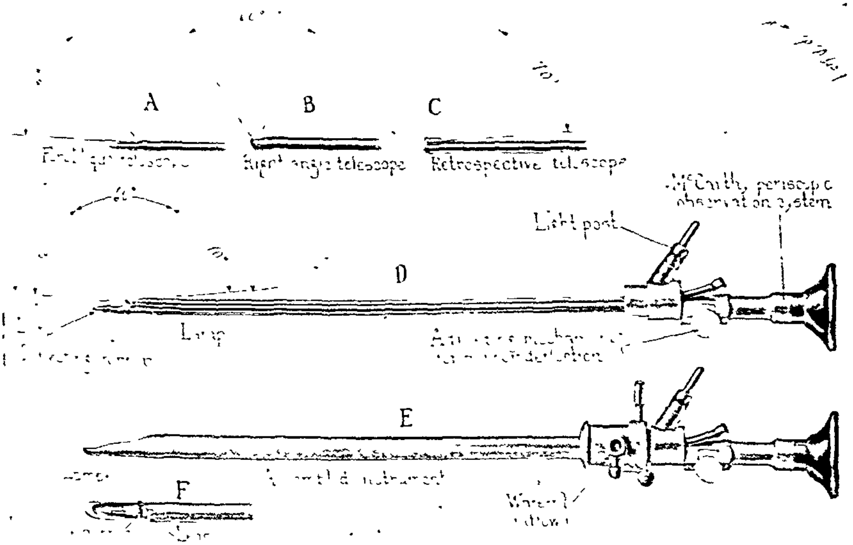

FIG. 2. McCarthy foroblique retrospective panendoscope. Illustration demonstrates visual field and component parts of instrument.

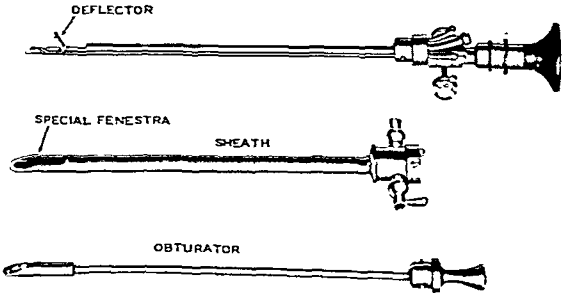

FIG 3. McCarthy deflecting panendoscope with component parts

VISUALIZED ELECTROTOME

This too, has been the instrument that served a purpose for which it was not designed. It has brought to the doors of many of our colleagues more folding money than they had ever anticipated. It too, was susceptible of improvement. Electronic or remote control provides a green and a red button, incorporated in the instrument, which obviates the need for the awkward footswitch, shortens operating time, minimizes bleeding, with their co-incidental advantages. Another defect is the more than occasional postoperative incontinence. To obviate this serious defect, it seemed that an especially designed sheath so constructed as to engage the supra montaine prostate, push it away from the external sphincter and then excise it might provide the answer. It did seem so in actual practice, but the current not only removed the prostate, but also disintegrated the acuminate terminal in the floor of the sheath. This defect has been correct with a terminal that is resistant to the high velocity current. Another application for this special sheath is the fixation of vesical growths prior to excision—this while not always necessary is at times desirable. It is merely presented for your consideration as it has not yet been accorded the acid test of time. Other advances with this instrument have been technical and clinical.

Believe it or not, we show here a 12F resectoscope (fig. 4) which though in the same situation as the last mentioned development, seems to be something more than a toy, and it may fill an occasional void. As a matter of fact, one of my associates, Dr. Kramer, brought a 12 year old boy with complete retention due to a middle lobe prostate obstruction. Through a perineal incision and a 16F resectoscope, he was able to perform a satisfactory resection on this patient.

Now for the clinical side. Some several years ago, we developed, in our department, a method of arrestation of bleeding following suprapubic prostatectomy. The patient was placed in the cystoscopic position which, incidentally, is much better for enucleation than the dorsal. He was prepared above and below, the prostate enucleated intra-urethrally, the cavity packed with very hot gauze. After these steps, a visualized electrotome was passed per urethram and the arteriolar bleeders electrocoagulated under perfect vision, and the operation was completed without packing or traction bag. This seemed to me a rational as well as the first precision method of conducting such operation. Only a few were carried out in this manner as I could not sell the idea to my chief departmental associate, though the objection advanced seemed to me insufficiently weighty—"that injury to the prostatic urethra might occur in the passage through the weakened canal." It then remained dormant until Dr. A. Hyman of our city, a urological surgeon of wide experience, took up the procedure. He recently reported some thirty odd cases carried out by this method with complete closure; one mortality, a coronary. The shortest healing time was 7 days and the average 12. I am not, however, an advocate of complete closure following suprapubic prostatectomy. For the benefit of some ill informed commentators who have been a bit strabismic in their recognition, and for the purpose of the record, all the foregoing with the exception of the application of remote control, has directly resulted from our research.

Some in this audience were present when we first demonstrated the feasibility of prostatic resection with a simple hand loop through a panendoscope, provided with a neutral terminal on the sheath of that instrument.

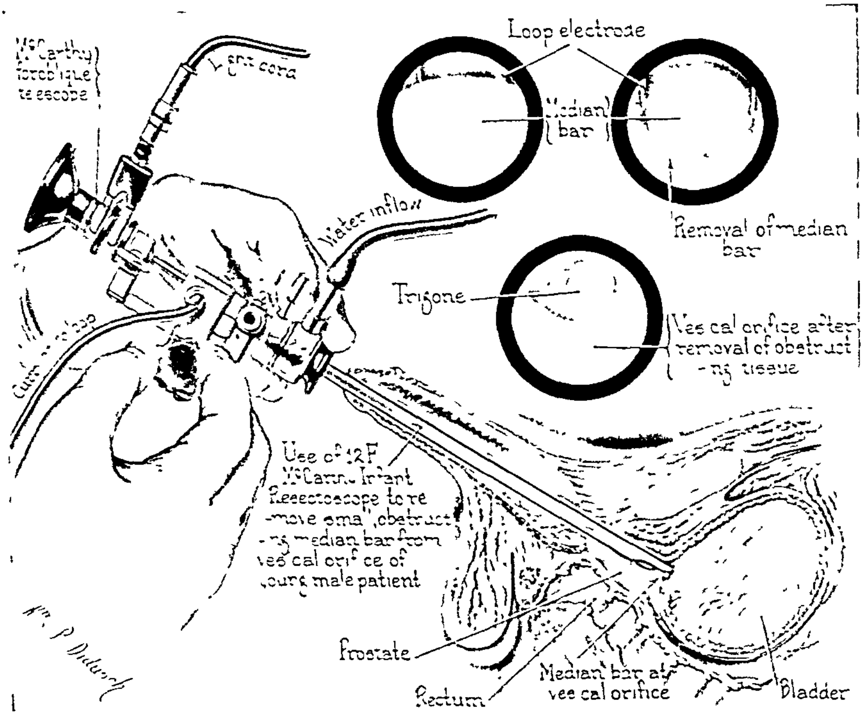
McCarthy foroblique telescope
Lamp cord
Water inflow
Loop electrode
Median bar
Removal of median bar
Trigone
Vesical orifice after removal of obstructing tissue
Use of 12F McCarthy Infant Resectoscope to remove small obstructing median bar from vesical orifice of young male patient
Prostate
Rectum
Median bar at vesical orifice
Bladder

FIG. 4. Shows on section, removal of small, obstructing median bar with 12F McCarthy resectoscope. Inserts are views obtained during operation.

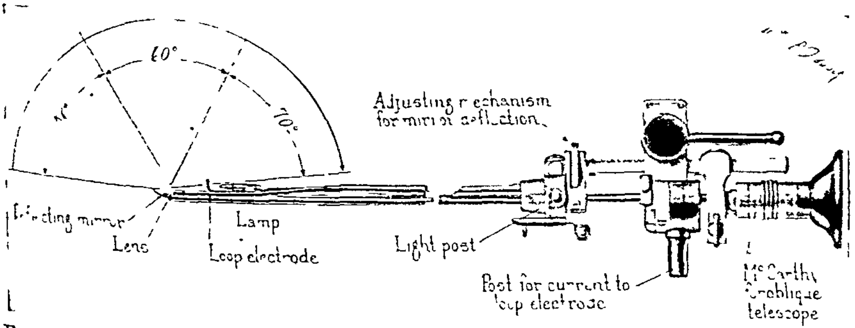
60°
70°
Reflecting mirror
Lens
Lamp
Loop electrode
Adjusting mechanism for mirror deflection
Light post
Post for current to loop electrode
McCarthy foroblique telescope

FIG. 5. McCarthy foroblique retrograde resector. Illustration demonstrates visual field and relation of loop electrode to lens and reflecting mirrors.

CATHETERIZATION OF EJACULATORY DUCTS

Probably the majority of urologists are content to permit this occasional though potential focus of infection to continue its residence in the field of conjectural obscurity. A notable few, however, have shown the perspicacity in following through. Notable among such is Dr. Robert Herbst of Chicago, whose experience in his many cases has been enlightening. Complacency is the anethema of progress. If contented with one's self on this matter, at least give younger associates an opportunity to look into it. Years ago, we published a communication on this subject, on methods of collecting vesicular fluid for culture, by the injection of normal salt solution. Hemospermias were treated successfully by instillation of dilute solutions of silver nitrate. We even tried insemination with ejaculate (vicariously obtained) diluted the same with buffer solutions of phosphate and glucose in incubators, injected it into azospermic vesicles and recovered the same after 48 hours, actively motile. The "bug" in this experiment was the presence of blood and pus cells. All this study needs is the sterilization of the spermatozoa without their destruction. Perhaps the newer antibiotics may provide the answer.

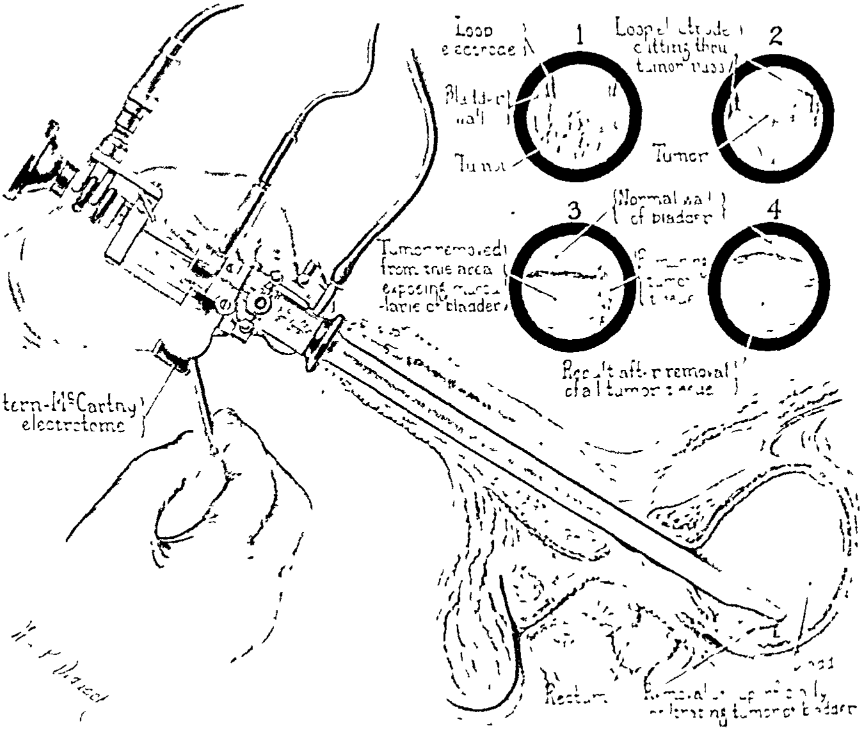
Loop electrode
1
Looped electrode cutting thru tumor mass
2
Bladder wall
Tumor
Tumor
3
Normal wall of bladder
4
Tumor removed from this area exposing muscularis of bladder
Result after removal of all tumor tissue
Stern-McCarthy electrotome
Rectum
Removal of superficially infiltrating tumor of bladder

FIG. 6. Shows, on section, McCarthy resectoscope in removal of superficially infiltrating tumor of bladder. Inserts are views obtained during operation.

RETROGRADE PROSTATIC RESECTION

A considerable sum of money has gone into this complex subject on the part of my collaborators. It had seemed to us we were doing a *retrograde operation* with foreoblique vision. Perhaps both types may provide the answer. It has not as yet received our complete approval. See *figure 5*.

THE UPPER URINARY TRACT

Here immediately before you is a most interesting field of precise endeavor for the elaboration of which the limits of this paper will not permit. Briefly, they comprise the ureteral catheter bag which can serve a number of purposes, such as blocking the renal outflow of one side during excretory urography as a substitute for pyelography, for precise renal pelvic lavage for a given period of time with the newer antibiotics under manometric regulation; as a supplement to constitutional treatment of incipient renal tuberculosis; and to facilitate location or dislocation of ureteral calculi; finally, in the biochemical disintegration of large renal calculi by similar methods, through nephrostomy self-retaining tubes with a prolongation down a part of the ureter to prevent the entrance of particles of stone; the objective here being, with a precise quantitative chemical examination of the stones together with their surface characteristics, an irrigating solution for the specific stones, reaching not only the pelves but the interstices of the calyces; again perhaps, under manometric pressure regulation; finally, employing the newer catheters that do not permit of crystalline deposits (polyethylene). The objective is to conserve kidney tissue, to convert a seemingly inoperable case into a potentially operable one. All these may, we hope, receive an assist from such gadgets as a visualized ureteral forceps, a renoscope, a renal pelvic visualized forceps, and the fantastic microwaves transmitted without wires, deflected into interior organs through a magnatron sheath by an electromagnetic field, an electronoscope without lenses, the interior steps being projected on a magnetized screen outside the body. These latter complex electrophysical concepts are the brain children of my scientific collaborator, Mr. Frederick J. Wallace.

BLADDER NEOPLASMS

Here again, in certain clinics, there is an over-emphasis on endoscopic electrocoagulation, in others the same stress on uretero-intestinal anastomosis. In the latter we hear and read more about new techniques than late end results. A case of endoscopic electrocoagulation with a fatal termination from pelvic cellulites induced the writer to find a better approach to some of these growths short of total cystectomy. A case report will illustrate the point. The patient, a man in the sixties, had six discrete papillary tumors. Total cystectomy was recommended. As an alternative the opinion was expressed that we might be able to carry him along for a number of years without the more radical procedure. The latter was accepted. The bladder was completely mobilized. A laparotomy pad was placed between the bladder and rectum, the growths on the mobile portion of the bladder excised with loop electrodes with remote control buttons. The two growths on the trigone were excised down to the musculosa, the base intensively electrocoagulated. This patient after 2½ years is microscopically, endoscopically and symptomatically free of growth (papillary adenocarcinoma).

Surgical urology is pretty much the same in large centers here and abroad. Instrumental precision urology is something else. It is in this field that American urology has been blessed by a succession of technical geniuses, first, Reinhold Wappler, then Frederick Wappler, and now Frederick Wallace. It is through the collaboration of such men who were and are scientists first and business men after, that world urology has been attracted to our doors.

2 E. 54th St., New York, N. Y.

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ELECTROSURGICAL COMPLICATIONS OF TRANSURETHRAL PROSTATIC RESECTION

JAMES H. SEMANS

The performance of the cutting and coagulating currents during transurethral resection of the prostate is an important factor in the success or failure of the operation. The undesirable effects are both immediate and late. If the current coagulates the tissue excessively, the surface becomes charred and is a poor electrical conductor. A deeper cut in the same area is hindered. Later, this residual necrotic tissue may become obstructive and chronically infected (fig. 1).

Too little coagulation by the cutting current results in excessive bleeding during operation. The blood converts the irrigating fluid from a nonconductor into a conductor. Much of the cutting current is then diverted from the prostatic tissue and diffused throughout the fluid in the urethra and bladder. In addition, visibility is impaired. These and other difficulties occur frequently during electrosurgery of the prostate. The details of technique which will prevent these errors, therefore, deserve attention.

Unsatisfactory cutting is most often caused by a lack of current at the point of contact between the cutting loop and prostatic tissue. Reasons for this decreased flow of current will be briefly mentioned and illustrated.

Insufficient flow of current may originate at the power company. For example, if industry in a community is using current in large quantity at a time of day when transurethral surgery is in progress, the voltage may be too low for the electrosurgical unit.

The wire between the wall socket and the electrosurgical unit may be too small to supply adequate voltage.

Other electrical devices, such as an infra-red lamp, a light bulb of high wattage, elevators and x-ray apparatus, are occasionally attached to the same circuit as the unit. Significant deficits in voltage will occur when these appliances are in use.

In order to detect these faults, it is advisable to measure the flow of current by a voltmeter. This is attached, if possible, on the same switch plate from which the electrosurgical unit receives its current. The voltage is read during an operation, while cutting is in progress. If the reading is low, either the power company must increase its output, or the other appliances must not be used during transurethral surgery. The number of volts necessary varies with the make or model of the instrument. Most units require 115 volts (fig. 2).

Satisfactory cutting also depends upon the electrical contact of the connecting cords between the wall, the electrosurgical unit, and the patient. Testing these cords and their points of attachment is the first maneuver for the operator or his assistant, when the current fails to flow well (fig. 3, A).

The continuity of the wires within these cords, as well as the electrical contact, can be tested readily. By touching the clip on the indifferent cord to the male tip

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Read at annual meeting, Southeastern Section, American Urological Association, Gulfport, Miss., February 3, 1950.

of the active cord, with both cords in place and the current flowing, brilliant sparking is produced, if the wiring is intact. Since the rubber insulation is elastic, a break in the wires may be demonstrable only by stretching the cord. This type of defect may produce unexpected failure of cutting as the resectoscope is moved. A common site of break in the wire is near the connection between the cords and their jack plugs (fig. 3, *B*).

A defect in the rubber insulation is best demonstrated by adjusting the coagulating current to the highest reading used in operations, depressing the foot pedal and passing a hemostat over the surface of all cords. The appearance of a spark will often identify the break in insulation. Too high a setting may produce carbonization of the insulating material and a short circuit (fig. 3, *C*).

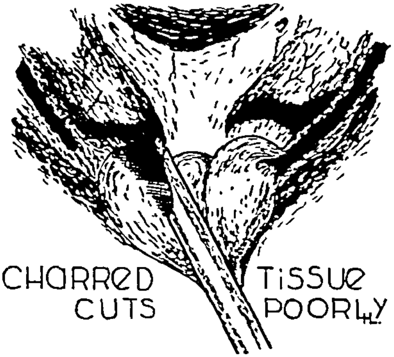

FIG. 1. Charring of tissue, caused by excessive use of spark gap current, resists deeper cutting.

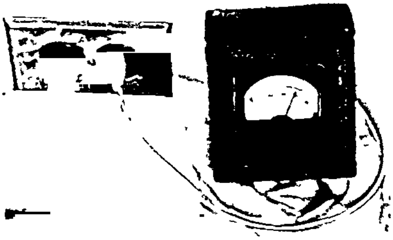

FIG. 2. Voltmeter and electrosurgical unit attached to same switch plate. Reading, made during cutting, measures house current.

The indifferent electrode beneath the patient interferes with cutting, if conductivity is not sufficient. A broad, flat, metal plate provides satisfactory contact. This is preferable to the old type of lead foil, which soon becomes wrinkled. Its irregular surface has been reported to produce burns, because of excessive concentration of current at isolated points on the skin.

The connection between the cord and this electrode should be separated from the patient. The accidental detachment of the cord by the weight of the patient thus is prevented. A burn has been reported between the clip of the electrode and the patient's skin, when sufficient distance did not exist between the two (fig. 3, *D*).

Another cause of poor conduction is the presence of dried lubricating jelly, vaseline, sheets and other nonconductors on the surface of the indifferent electrode. *No lubricant is necessary.* These should be removed from the indifferent electrode before operation is begun (fig. 4).

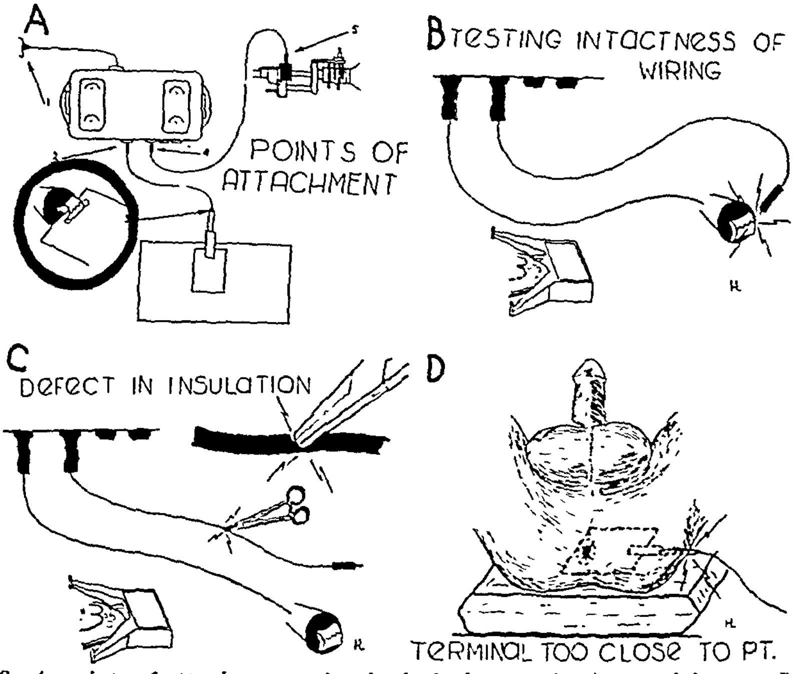

FIG. 3. *A*, points of attachment to be checked when cutting is unsatisfactory. *B*, active sparking, with current flowing, shows that all wiring between electrodes and wall socket is intact. *C*, sparking through defect in insulation, with current flowing. *D*, short circuit between electrode and patient's skin, a cause of thermal burn.

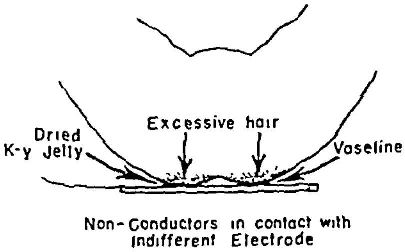

FIG. 4. Excessive hair, dried K-Y jelly or vaseline inhibits satisfactory electrical contact.

An excessive amount of hair on the buttocks may insulate the patient from the underlying electrode sufficiently to produce a poor flow of current. This is corrected by shaving this area before operation (fig. 4).

The irrigating fluid must be a nonconductor, so that the current will be concentrated where the loop is in contact with prostatic tissue and not diffuse itself throughout the fluid in the bladder. This undesirable effect is produced by allowing the water in the bladder to become excessively bloody. Irrigating fluid of high mineral content ("hard water"), normal saline, or water to which large amounts of purifier have been added as a measure of municipal sanitation, also disperse the current and hinder cutting (fig. 5, *A*).

Glucose or amino acids in the fluid do not disperse the current.

A broken cutting loop has the same dispersing effect on the flow of current (fig. 5, *B*).

A gap left between the cutting loop and its socket in the working element may be sufficient to interfere with cutting and produce an odor of burning. This is eliminated by being certain that the pointed end of the loop is pushed completely into the socket before the set screw is tightened (fig. 6).

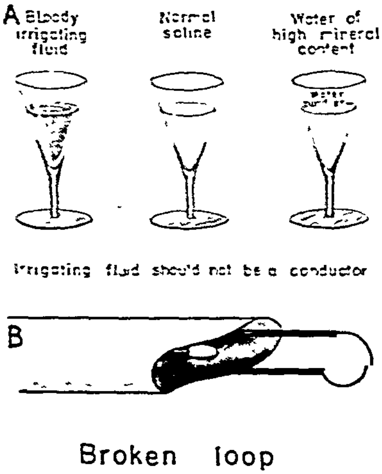
A
Bloody irrigating fluid
Normal saline
Water of high mineral content
Irrigating fluid should not be a conductor
B
Broken loop

FIG. 5. *A*, excessive blood, normal saline or water of high mineral content, disperses current and inhibits cutting. *B*, broken loop disperses current, interfering with cutting.

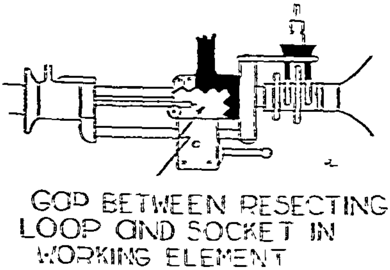

FIG. 6. Gap between cutting loop and socket in working element prevents free flow of current and causes carbonization.

The types of cutting current differ in the various commercial units. In general, the current is generated by either a tube or a spark gap, or by the combination of both. It is not within the scope of this discussion to describe the electrical and mechanical principles peculiar to each unit. This information is available from the manufacturers. However, their effect on the tissues is pertinent.

The importance of producing as little necrosis as possible has already been emphasized. This is accomplished by destroying a minimum of tissue. Occasionally, a stream of blood can be used as a conductor and bleeding stopped by the tube cutting current (fig. 7, *A*) without the use of the coagulating (spark gap) current. Remaining tags of mucous membrane are also most easily excised by using the tube current alone (fig. 7, *B*).

Hemostasis by excessive electrocoagulation leaves necrotic tissue. Bleeding from the venous plexus of the prostatic capsule is better managed by the application of topical thrombin or tamponade with the hemostatic catheter at the end of operation, as suggested by Nesbit.

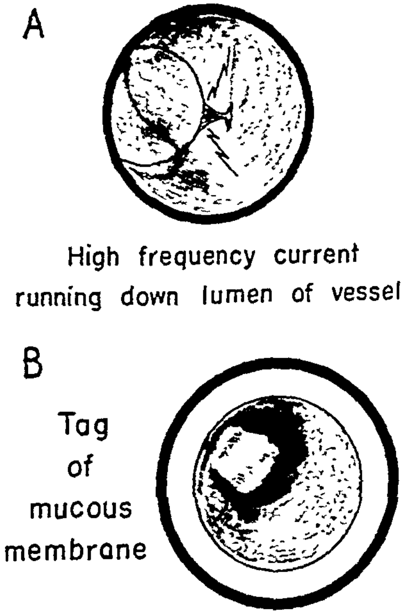

FIG. 7. *A*, method of hemostasis, useful when minimal necrosis is essential. *B*, tag of mucosa requiring tube cutting current for removal.

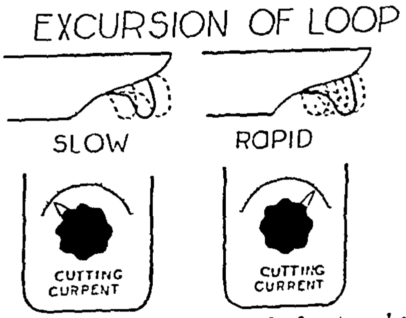

FIG. 8. Showing relationship between speed of cut and setting on dial.

The settings on the dials of various units differ, and should be adjusted according to the instructions for the particular model in use. It is important that the surgeon know that the speed of electrocutting is dependent upon the intensity of the high frequency current. Therefore, as the speed of excursion of the loop increases, a higher setting is necessary. The loop will then meet less mechanical resistance. Conversely, if the loop is moved slowly, the setting should be reduced in order to prevent excessive dehydration and necrosis. The correct setting is that which produces the least mechanical resistance to excursion of the loop without excessive bleeding or charring of tissue (fig. 8).

The hemostatic effect of the cutting current is increased either by a slower excursion of the loop, or by the introduction of a current from a spark gap, when the means for this is provided by the electrosurgical unit. Either maneuver becomes desirable to counteract increasing vascularity, as the prostatic capsule is approached.

One of the unsolved problems is the prevention of postoperative bleeding. This is produced by separation of the coagulum from the cut surface of the vessel, or by postoperative increase of intravascular pressure. The risk of re-

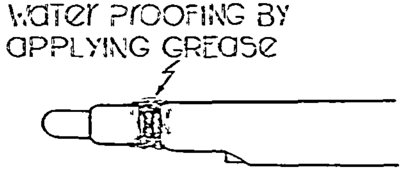

FIG. 9. Grease applied for waterproofing, after bulb has been partially screwed into socket.

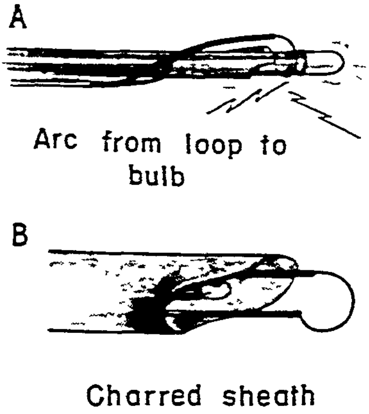

FIG. 10. A, short circuit between cutting loop and light bulb. B, charring of sheath produced by high frequency current.

peating anesthesia and instrumentation to stop bleeding in older patients is indication for further study of this problem.

There are at least 5 causes for a dimly burning light bulb during operation. If grease has not been used to waterproof the connection of the bulb to the telescope, moisture may produce interference with the flow of current. This is prevented by applying grease to the threads of the light bulb, while screwing it into the telescope. In this manner the grease seals the connection without entering the socket (fig. 9).

A short circuit lessens the current passing to the light bulb. If the foot pedal remains depressed at the end of the excursion of the cutting loop toward the operator, an arc of electricity may pass between it and the telescope (fig. 10, A).

If the high frequency cords cross or parallel closely the light cord, bulbs may burn out.

A wire in the light cord within the connector may be broken.

The final cause is approaching termination of the life of either the bulb or the battery.

Failure to remove the foot from the pedal promptly at the end of each excursion sometimes causes the high frequency current to char the sheath of the resectoscope. The charred sheath becomes a conductor of electricity. Unnecessary necrosis of adjacent tissue and short circuiting result (fig. 10, *B*).

As high frequency currents of greater intensity are adopted, formerly satisfactory sheaths may show charring. A more resistant material for the sheath will become necessary.

In addition to a poor flow of current, there are minor complications related to details of technique. One of these is the occurrence of a spark between the instrument and any conducting surface such as the operator's head, his hand or the patient's leg. This is produced by discharge of an electric field built up around the resectoscope. This field of current is occasioned by the intense high frequency current necessary for adequate cutting. The cause of the sparking may be the rubber glove on the operator's hand gripping the resectoscope. The glove, being a nonconductor, interferes with grounding. The field produces enough current to jump the gap between the instrument and the nearest conducting surface. If the glove is removed, this difficulty is eliminated (fig. 11).

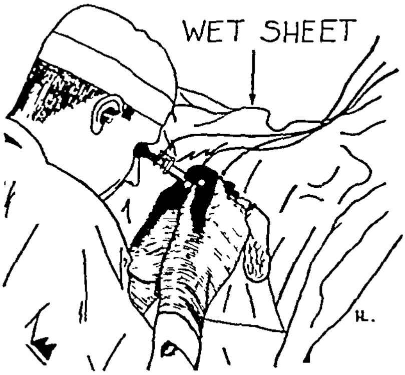

FIG. 11. Sparking from resectoscope to operator's head or patient's leg, eliminated by removal of rubber glove.

A rare, but serious complication is caused by wear in the insulation within the rheostat, when this apparatus is used in illumination of the light bulb. Lack of insulation allows the full voltage of the house current to travel through the rheostat and light cord to the patient. This may be sufficient to propel him from the table. The rheostat normally reduces the voltage from 115 to 6 volts or less before it enters the light bulb. The use of a battery, in preference to a rheostat connected to the house current, is strongly recommended (fig. 12).

SUMMARY

Electrosurgical factors complicating transurethral resection of the prostate are mentioned:

A. Insufficient flow of the cutting current. Causes of this include: continuous low voltage to the electrosurgical unit from the power company or from a connecting cord carrying wire of small caliber; intermittent low voltage because of other appliances attached to the same circuit as the electrosurgical unit; defective electrical contact caused by loose jack plugs, broken wires and defective insulation in connecting cords; a nonconducting surface between the patient and the indifferent electrode; irrigating fluid of high electrical conductivity (blood, mineral salts, water purifier); a defect in the resecting loop or its insulation; a gap between the resecting loop and its socket in the working element; electrical resistance of charred tissue following excessive coagulation; inadequate power setting for the speed of excursion of the resecting loop.

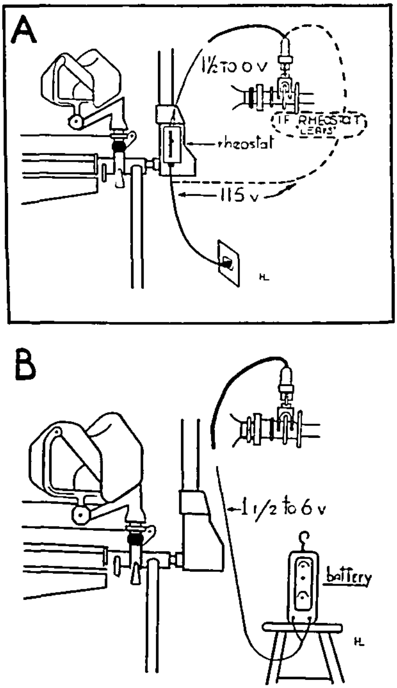

FIG. 12. *A*, rheostat reduces 115 volts to safe levels of 1½ to 6 volts for illuminating light bulb. Defective insulation in rheostat allows 115 volts to pass to patient. *B*, battery of 6 volts replaces rheostat and avoids hazard of leakage in rheostat.

B. Dim illumination by the light bulb. Causes: moisture within the socket; short circuiting between the resecting loop and the telescope; light cord crossing or closely parallel to cord carrying high frequency current; a loose or broken wire in the light cord; approaching termination of the life of either the bulb or battery.

C. Other complications include: short circuiting and necrosis of tissue caused by charring of the sheath; sparking between the resectoscope and conducting surfaces on the patient or operator; a rare, but serious accident produced by a defective rheostat, and avoided by the use of a battery for illumination.

Means of preventing and correcting numerous complications are recommended.

The author gratefully acknowledges the excellent illustrations by Dr. Henry La Guette and Miss Helen Mackay, and also the indispensable cooperation of the following manufacturers and their representatives: American Cystoscope Makers Incorporated, Mr. Frederick Wallace and Mr. Arnold Kleine; the Birtcher Corporation, Mr. C. J. Birtcher; the Liebel-Flarsheim Company, Mr. John Otto and Mr. Fred O'Connor.

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REFERENCES

Barnes, R. W.: Endoscopic Prostatic Surgery. St. Louis: C. V. Mosby Co., 1943.
Nesbit, R. M.: Transurethral Prostatectomy. Springfield, Ill.: C. C. Thomas, 1943.
Weyrauch, H. M., Bassett, J. B. and Berger, M. M.: High frequency currents for transurethral prostatectomy. J. Urol., 61: 371, 1949.

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USE OF UREA SOLUTIONS AS IRRIGATING FLUIDS

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All of us are cognizant of the service rendered our specialty by Creevy, Foley, Emmett and McLaughlin in 1946 when they independently recognized the occurrence of hemoglobinemia and hemoglobinuria as disturbing complications of transurethral resections. Up to that time either distilled or tap water was used routinely as an irrigating fluid during transurethral resections. Many resectionists had occasionally observed postoperatively an unexplained reduction in red blood cell concentration which was often accompanied by decrease in renal function, oliguria, anuria and sometimes even death in uremia. Creevy, in his thorough survey of the subject, pointed out that an irrigating fluid consisting of water quickly hemolyzed red blood cells on contact. These observers recognized that the irrigating solution after contact with blood in the bladder contained varying concentrations of free hemoglobin depending upon the amount of bleeding and that this solution often gained access to the general circulation through open vascular communications established in the prostatic bed during operation.

The operator who attempted to do a complete removal of the hyperplasia was confronted with the risk of exposing large venous sinuses and allowing a hemolyzed solution to enter the circulation. Landsteiner, using sodium salicylate in the irrigating fluid, estimated that on occasion as high as 1000 cc fluid might enter the general circulation. The irrigating fluid was also hemolytic after it entered the patient's blood stream and resulted in the intravascular liberation of additional amounts of hemoglobin. The latter is responsible for the major portion of the free intravascular hemoglobin rather than that which enters the blood stream with the irrigating fluid. We have measured the amount of hemoglobin in the fluid which might escape from the bladder into the blood stream. The hemoglobin contained would result in a serum hemoglobin of only 116 mg. per cent at the maximum. These determinations were made on irrigating fluid at the bloodiest stage of the transurethral resections. It is obvious that this would account for only a relatively small fraction of free hemoglobin present in the blood stream in some recorded cases of hemoglobinemia following transurethral resection and that the major portion of the hemolysis is due to the hemolyzing action of the solution after it has entered the circulation.

The use of a 5 per cent nonhemolytic solution of glucose as an irrigating fluid in order to prevent hemolysis was suggested to Creevy by Ebert and was later instituted by many operators. The sticky properties of this solution and the reduction of vision caused many who adopted glucose to revert to water. Other innocuous and nonelectrolytic substances which would render irrigating fluids nonhemolytic were soon suggested. Such substances as amino acids, hex-

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Hot Springs, Va., March 25, 1950.

itols, lactose and disaccharides were suggested inasmuch as they were nonelectrolytes and the red blood corpuscle is not readily permeable to these substances. In the December 1948 *Journal of Urology* Ebert suggested the use of an urea solution as a logical and safe substitute for water as an irrigating fluid. It was economical, easily prepared and did not obscure vision. If ingress into the circulation occurred it was a constituent of normal blood. He stated that a 1.8 per cent solution was isomotic, and also isotonic with physiologic saline. In the November 1949 *Journal of Urology* he again reported on urea and its successful use in 295 successive transurethral resections. In 5 cases of periprostatic extravasations with urea solution recovery occurred in each instance. It was his opinion that the presence of urea in the irrigating solution contributed a large part to the recovery of these patients. In 3 other patients subjected to prolonged fulguration with open venous sinuses he noted serum hemoglobin levels as high as 600 mg. even though urea solutions were used. Ebert further stated at that time that a 0.9 per cent urea solution was preferable to his original 1.8 per cent solution. He had found the latter was more nearly isotonic although only one-half isomotic. With this 0.9 per cent urea solution he had observed no hemolysis.

As a result of Ebert's articles we abandoned the use of distilled water and adopted a 0.9 per cent urea solution with a considerable sense of security. The following case in which 0.9 per cent urea solution was used soon convinced us that urea offered no protection and was in reality just as hemolytic as distilled water.

J. N. B., Univ. of Va. Hosp. No. 289382, a 74 year old man, was admitted in acute retention with adenocarcinoma of the prostate. During the course of a subsequent transurethral resection it was realized that a large venous sinus in the capsule had been entered. The operation was pursued some 10 minutes longer to its completion during which time the blood pressure gradually rose to a systolic of 220 mg. of Hg. This was followed by a chill which so characteristically follows the release of free hemoglobin within the blood stream from whatever cause. At the end of the operative procedure freshly drawn blood revealed free hemoglobin to be grossly present in the serum. On chemical determination this was found to be 780 mg. per cent (serum). The patient was given intravenous procaine and observed very carefully as to any tendency to shock. A 500 cc blood transfusion was administered and no evidence of vascular collapse developed. In spite of this large amount of hemoglobinemia there was not the slightest indication of renal damage in the convalescent period. The blood urea remained normal and the first day after operation the patient excreted 2100 cc of urine with a restricted 1400 cc intake. In the ensuing days normal amounts of urine were excreted. The patient made an entirely uneventful recovery.

One ml. of hemolyzed blood results in a serum level of approximately 5 mg. per cent. According to calculation our patient had hemolyzed 156 cc of whole blood. Other observers have found similarly high levels without evidence of renal damage and conversely low levels of hemoglobinemia have been associated with fatal anuria.

We continued to use urea in approximately 20 additional patients following the case just reported, and of these cases approximately one-half showed hemoglobinemia visible to the naked eye, i.e. in excess of 30–40 mg. per cent. One patient in this group showed a serum value of 250 mg. per cent while the remainder were of a low order (less than 100 mg. per cent of free hemoglobin). Hemoglobinemia was occurring with the same frequency as we had found when we were using pure water several years previously. Figure 1 is an example of the findings in a case of intravascular hemolysis following transurethral resection in which distilled water was used as an irrigating fluid. In this case large venous sinuses were encountered in the prostatic capsule. Immediately following operation the serum was grossly colored and the hemoglobin was 268 mg. per cent. It can be seen from this figure that the hemoglobin excretion rate is expressed as an exponential curve.

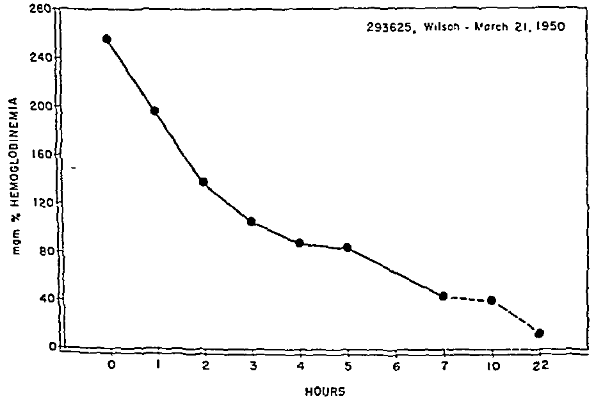

FIG. 1. Illustrating clearance of free hemoglobin following transurethral resection with intravascular hemolysis as a result of using distilled water as irrigating fluid. Blood drawn immediately following completion of operation showed serum to contain 268 mg. per cent of free hemoglobin. Blood serum examined at hourly intervals showed free hemoglobin being cleared at rapid rate. It can be noted that rate of disappearance forms an exponential curve.

The experience in the reported case stimulated us to reappraise the use of urea as an irrigative fluid. Normal blood was tested in vitro in combination with the various solutions as depicted in figure 2. In tube No. 1 is a 10 cc solution of 1.8 per cent urea as recommended by Ebert to which was added 1 cc of fresh whole blood. It is obvious that complete hemolysis occurred. In tube No. 2 there is a solution of 0.9 urea and 1 cc blood again showing hemolysis. These and other concentrations of urea solution were tested for hemolysis many times. A complete hemolysis similar to that of blood plus distilled water as shown in the test tube No. 3 always followed. In test tubes No. 4, 5 and 6 there is no hemolysis and the intact red cells are at the bottom. Tube No. 4 contains a solution of .45 per cent sodium chloride and 0.9 per cent urea. The absence of hemolysis here demonstrates that urea is not hemolytic and that it is the tonicity of the solution which prevents hemolysis. In tube No. 5 and 6 are solutions of 2.2 and 1.1 per cent glycine respectively. Glycine never produced hemolysis when tested in this manner.

It was of interest to speculate what would happen with fluids which escaped into the general circulation. Figure 3 depicts the results of various solutions on whole blood. Each test tube contains 10 cc of fresh blood. In tube No. 1 two cc of distilled water was added and gross hemolysis is evident. The supernatant serum in this tube contained 414 mg. per cent of free hemoglobin. In test tube No. 2 there was added 2 cc of 1.1 per cent glycine with no visible evidence of hemolysis. Determination showed a trace of free hemoglobin which is within the accepted limits of laboratory error. In tube No. 3 containing whole blood we added 2 cc of 0.9 per cent urea solution and again we have frank hemolysis with the supernatant serum containing 420 mg. per cent, almost precisely the same amount of free hemoglobin as the solution of distilled water as shown in test tube No. 1.

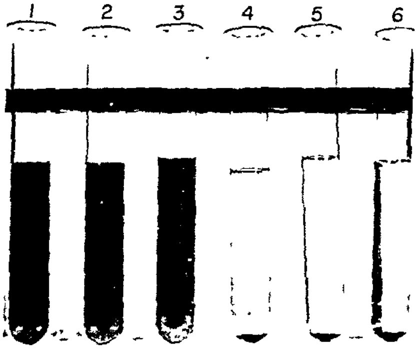

FIG. 2

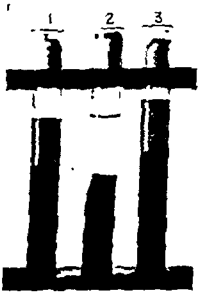

FIG. 3

FIG. 2. Illustrating experiments appraising action of urea on red cell corpuscles. Test tube 1 contains a solution of 1.8 per cent urea to which has been added 1 cc fresh whole blood. It is apparent that complete hemolysis has occurred. Test tube 2 contains 0.9 per cent urea and 1 cc of blood resulting in complete hemolysis. Test tube 3 shows a similar complete degree of hemolysis when blood is added to distilled water. Test tube 4 contains, in addition to blood, 0.9 per cent urea and 0.45 per cent of sodium chloride. Red blood corpuscles have settled to bottom with complete absence of hemolysis, demonstrating that urea itself is not hemolytic, and that it is tonicity of solution which prevents hemolysis. Test tubes 5 and 6 contain 2.2 and 1.1 per cent glycine respectively, demonstrating absence of hemolysis with the amino acid, glycine.

FIG. 3. Illustrating what happens when fluids escape into general circulation. Each tube contains 10 cc fresh blood. In test tube 1, 2 cc distilled water produced gross hemolysis and supernatant serum contained 414 mg. per cent of free hemoglobin. In test tube 2, 2 cc of 1.1 per cent glycine when added to whole blood produced no evidence of hemolysis. In test tube 3, 0.9 per cent urea solution was added to whole blood and again gross hemolysis occurred. Supernatant serum contained 420 mg. per cent of free hemoglobin. These experiments demonstrated that distilled water and urea solutions are comparable hemolytic agents while glycine is nonhemolytic.

It is evident from these and other tests that urea alone is not isotonic in any concentration as regards the erythrocyte. Tonicity requires the presence of an impermeable membrane. It is well known and demonstrated above that the red blood cell is freely permeable to urea so that no effective osmotic force with regard to the red cell is exerted by urea in solution. The water of a urea solution enters the erythrocyte rapidly resulting in swelling which stretches the interstices of the cell membrane and allows the escape of hemoglobin. Urea solutions are therefore entirely useless and offer no protection from hemolysis to the patient. Their widespread usage among operators for this reason should be decried. We believe that Ebert's deductions concerning the protective effect of urea solutions in his series of 295 cases are not valid and that his good results are more likely due to excellent postoperative management of the patient.

We then abandoned the use of urea solutions and substituted a 1.1 per cent glycine solution as an irrigating fluid. With the use of glycine we have seen no gross evidence of hemolysis following transurethral resection. Serum determinations of free hemoglobin showed small values in a few sera ranging from 10 to 30 mg. per cent but this is of no significance and within the limit of error of collection and determination.

At our clinic we routinely attempt, except under mitigating circumstances, to remove all glandular tissue and expose the capsule. Venous sinuses are frequently encountered in which there is a communication established with the vascular system. When a hemolyzing irrigating solution such as water was used an occasional patient with such a communication had a chill accompanied by a rise in systolic blood pressure with or without pain in the lower abdomen and followed by the appearance of free hemoglobin in the blood serum. This occurred with hemolyzing solutions even though we used the least amount of hydrostatic pressure in the irrigating system necessary to conduct the operation and achieve vision.

Since 1940, at this clinic, in patients undergoing transurethral resections, we have routinely administered 1500 cc (or recently 1000 cc) of 5 per cent glucose during the operation. Our reasoning at the establishment of this procedure was that the production of an active water diuresis during this type of operation was highly desirable as a protective measure for kidneys subjected to physiologic stresses incident to an operative procedure of this magnitude. We have carefully analyzed the 25 deaths that occurred during our last 1500-odd transurethral resections. During this series we have had but one fatality as a result of acute renal injury from intravascular hemolysis. It is significant that for some unexplained reason this patient escaped receiving the routine intravenous glucose during operation.

J. H. S., Univ. of Va. Hosp. No. 237046, a 73 year old man, was admitted in excellent physical condition and with good renal function. A transurethral resection was carried out without difficulty except that the operator noted a large venous sinus near the end of the procedure. Bleeding was troublesome and the operation was prematurely terminated. Immediately afterwards the patient experienced a chill on the table and the blood pressure gradually rose in a few minutes to 260/200. Neither sulfa drug nor whole blood was administered at any time. The patient developed anuria within the next 12 hours and died in uremia 4 days later with a blood urea of 190 and CO_2 combining power of 34.8. Pathological section (fig. 4) from the kidney revealed spotty degeneration of the tubules at various levels in the nephron.

We have attributed the absence of other fatal renal reactions in our series to the emphasis on active diuresis during the operative procedure even though until last year we continued to use hemolytic distilled water as an irrigating solution. From examinations of the blood sera postoperatively in 1947 we found the presence of free hemoglobin in a high percentage of sera postoperatively.

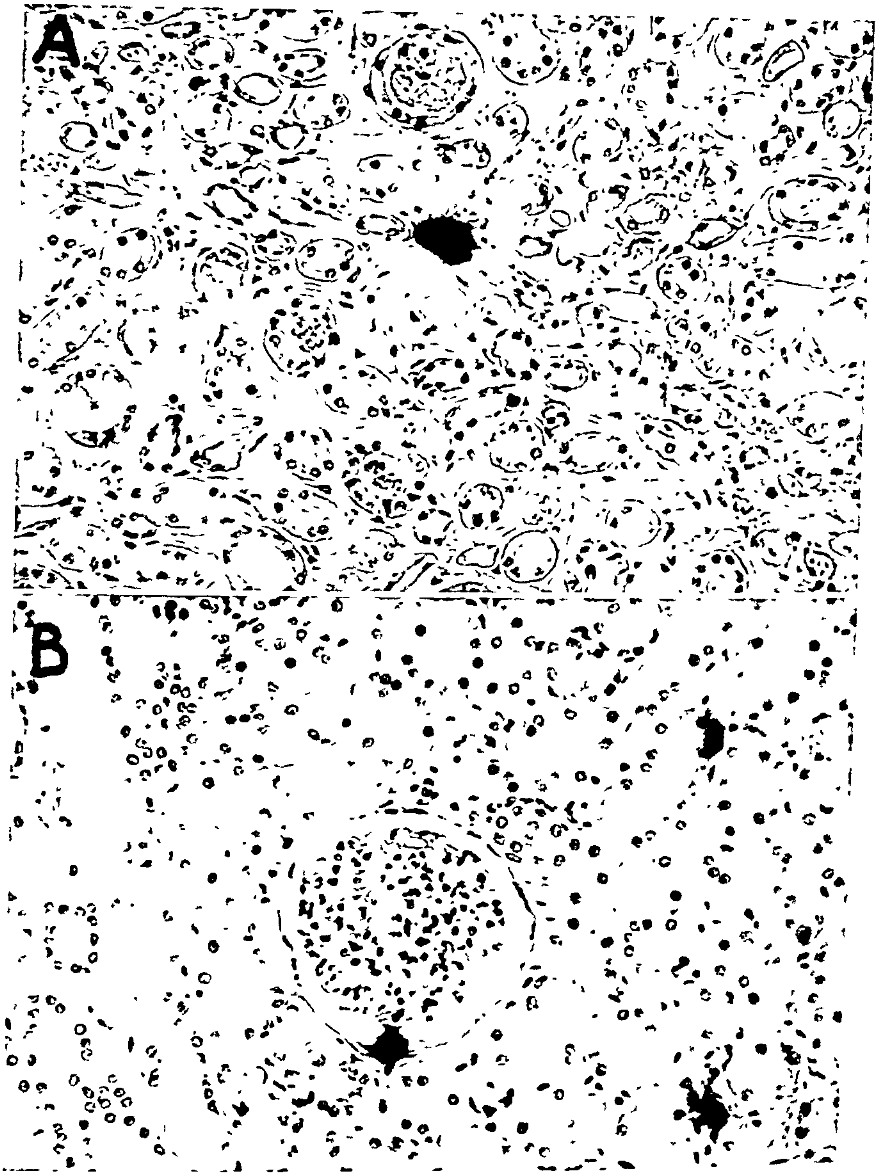

Fig 4. Histologic sections of a kidney obtained at autopsy from a patient who died following intravascular hemolysis due to use of distilled water as a transurethral irrigating solution Sections from both renal cortex and medulla are shown Changes are typical of so called lower tubular necrosis Many cortical tubules are necrotic and many contain an albuminous precipitate Section of medulla shows more casts than cortex, but in general casts present in this case were encountered less frequently than in case reported by Creevy

We now realize that one had best not depend solely upon active diuresis. It is also highly desirable to use isotonic solutions as the irrigating fluid during resections in order not to burden the nephrons with the excretion of large amounts of hemoglobin.

The lesion that occurs following hemoglobinemia during transurethral resections has become well known and has been described as "lower nephron nephrosis." The introduction of this term has been most unfortunate and is now considered to be a disservice to renal pathology. The lesion usually is a necrosis and dissimilar to that found in nephroses. More important, such renal lesions accompanied by anuria or oliguria are not limited to the "lower nephron," but involve also the proximal tubules. A more logical term, "acute tubular necrosis," is suggested. The type of renal insufficiency could be referred to as "acute tubular failure." Indeed, the glomerulus is even involved on occasion, in which the appropriate terminology would be "total nephron necrosis." Acute tubular necrosis accompanied by varying degrees of renal insufficiency is caused by a wide variety of inciting conditions all producing similar renal lesions and clinical syndrome. The condition may occur in the so-called pigmented states after hemolysis such as that following transurethral resection, mismatched transfusion, burns, many hemolytic toxins, and severe malaria. Among the common conditions resulting in a similar renal injury but not associated with hemolysis are sulfa poisoning, surgical shock, hepato-renal syndrome, various specific poisonings, yellow fever, etc.

It is not within the scope of this communication to fully discuss the pathogenesis of renal injury following hemoglobinemia from intravascular hemolysis or other causes, as a number of extensive reviews are available on this subject. A few generalizations, however would be in order. The part played by free hemoglobin and its excretion by the kidney in the production of such lesions is still obscure but the problem has evoked great interest and stimulated a large number of well designed, experimental undertakings. First, there is little evidence that moderate amounts of free hemoglobin or its oxy forms are toxic to the kidney when injected into man or various animals under experimental conditions. The uninjured and functioning animal and human kidney can filter, resorb and clear large amounts of injected hemoglobin without damage. If the mass of hemoglobin is extremely large, however, and suddenly appears in the blood stream, as following a mismatched transfusion, damage occurs in a high order of frequency. This one irrefutable fact confirms the participation of hemoglobin in the etiology of this specific renal injury on occasion. Small amounts of hemoglobin are injurious to the kidneys which are anoxic. It has been shown that renal anoxia may be produced as a result of reduced renal blood flow to the entire kidney or a reduced regional flow as described by Trueta. Vasospasm is a major cause of decreased renal blood flow and ultimately anoxia to the dynamic cells in the renal tubule. The vasospasm can result from a number of etiologic situations. Among the most important are shock, reduced blood volume, reduced hemo concentration, hemorrhage, antiphylaxis and nephrotoxins from a number of varied sources.

Factors other than anoxia may contribute to the injury. If during hemoglobin excretion there is a reduction in glomerular filtration and urine flow down the tubule, a mass of relatively stagnant hemoglobin within the renal tubules may be acted upon by either acid or alkaline filtrates. The result of such reactions is the formation of known ferrihemates which are cytotoxic on contact and result in direct injury to the cells of the renal tubules. In addition, varying numbers of nephrons may be obstructed by pigmented precipitates or casts.

Tubular injuries associated with hemoglobinemia in man or animals rarely occur unles a significant amount of hemoglobin appears in the serum or glomerular filtrate. However, Foy and others have pointed out the renal reaction may also occur under certain conditions with the intravascular hemolysis of small amounts of blood. If the other mitigating or complicating factors (anoxia, oliguria, aciduria, hemoconcentration, nephrotoxins, etc.) necessary to produce tubular damage are present to a marked extent then under such circumstances a small amount of free hemoglobin will produce a lesion. On the other hand, if these accessory injurious factors resulting in perturbed tubules or perturbed renal function are absent, then large amounts of hemoglobin are tolerated without injury. In summary the factors involved in producing acute tubular necrosis in hemolytic conditions are anoxia from a reduction of blood flow through areas of the kidney, excessive extremes of pH of urine, a reduced urine flow and the mass of hemoglobin pigment presented to the renal tubules for excretion at the precise and crucial time the other factors are in operation. It is evident that the ultimate outcome in any given instance may depend upon a fine balance between the degree of injury to the renal tubules and the amount of hemoglobin that is necessary for the kidney to excrete. When these two factors are operating together there is evidently a critical sum total which must be present in order for damage to occur. Diuresis or an increased rate of urinary excretion may protect the kidney by lowering the concentration of hemoglobin in the kidney.

From the standpoint of the clinician it is obvious that to avoid this specific renal injury in patients undergoing surgery the conditions or factors which are involved in the pathogenesis must be avoided or reversed. The first and primary denominator is to avoid situations which are likely to produce renal ischemia. Maintenance of blood pressure and blood volume and avoidance of prolonged surgery and undue trauma are of primary importance. The second factor is complete avoidance of hemolysis in either the bladder or blood stream and it is to this that this presentation has been especially directed. The third is to promote active diuresis during any exact period of time in which hemolysis or renal ischemia might occur. Diuresis increases the efficiency of the kidney to clear the mass of free hemoglobin and toxic substances at a greater rate of speed, resulting in less ultimate demand on the cells or tubules should then otherwise be laboring under toxic influences. A decreased concentration of hemoglobin within the tubules lessens the chance of injury from this cause.

Corcoran, Olsen, Lausen, Selkurt, Bywaters, Harrison, Maluf and others have shown that active diuresis tends to protect the renal tubules. The possible protective value of diuresis was first recognized during the last war in the bombing of London in a patient who was imprisoned under debris and suffered crushing injuries of the extremities. This released large amounts of heme-globin pigment into the blood stream and during its excretion fatal injury to the kidney with typical tubular necrosis and failure, oliguria and death were to be expected. This patient, who was imprisoned for a number of hours, was provided by helpful friends with an almost continuous supply of beer and thereby a very active diuresis was produced. The crushing injury to the extremities was of such an extent that a fatal acute tubular necrosis with anuria was considered inevitable. It did not occur and it was assumed that the diuresis was the factor in preventing the expected fatal renal lesion in this case.

Water diuresis is the best known and most physiologic way to increase urine flow. This is easily obtained by 5 per cent intravenous glucose which we have stressed during operation on patients who are somewhat dehydrated as a part of normal preoperative preparation. Lastly, electrolyte balance must be normal and undisturbed as experimental evidence has indicated that neither significant shifts in pH towards acidosis or alkalosis are desirable. If an acute tubular injury is once established in spite of all precautions treatment is entirely another problem not within the scope of this communication but to be sound it must be based upon known pathological physiology.

CONCLUSIONS

Solutions of urea for irrigating purposes during transurethral resection offer no protection against hemolysis, hemoglobinemia and hemoglobinuria and may result in possible severe or fatal renal reactions. Urea enters the red cell freely and produces no osmotic pressure relative to the red cell so that water of a urea solution also enters the red cell, resulting in a release of hemoglobin. It should be recognized that urea solutions act precisely as hemolytic distilled water and they should not be used with a false sense of security.

Intravascular hemolysis should be avoided whenever possible under all circumstances. Nonelectrolytic amino acids and sugars which are nontoxic and can be made into isotonic solutions are more logical and nonhemolyzing. Glycine (1.1 per cent solution) as suggested by Nesbit has been a very satisfactory substance in our hands and we believe that it deserves to supplant urea. It is economical, easily prepared and one of the building blocks of normal metabolism. If large quantities of this nonhemolytic solution enter the vascular system this natural amino acid will be metabolized into usable energy accompanied by an increased volume urine flow which in such case is essentially a physiologic "water diuresis."

The renal injury in hemoglobinemias is not always proportionate to the amount of hemoglobin released following resection or mismatched transfusion. It is often governed more by the extent and degree of complicating factors which tend to disturb renal function and reduce urine flow.

REFERENCES

Bing, R. J.: The effect of hemoglobin and related pigments on renal functions of normal and acidotic dogs. Bull. Johns Hopkins Hosp., 74: 161, 1944.

Bunge, R. G. and Barer, A. P.: Hemolysis during transurethral prostatic resection. J. Urol., 60: 121, 1948.

Bywaters, E. G. L.: Ischemic muscle necrosis; crushing injury, traumatic edema, crush *syndrome: Type of injury seen in air raid casualties following burial beneath debris.* J. A. M. A., **124:** 1103–1109, 1944.

Corcoran, A. C. and Page, I. H.: Post-traumatic renal injury, summary of experimental observations. Arch. Surg., **51:** 93–101, 1945.

Creevy, C. D.: Hemolytic reactions during transurethral prostatic resection. J. Urol., **58:** 125–131, 1947.

Creevy, C. D.: The importance of hemolysis during transurethral prostatic resection; a clinical investigation. J. Urol., **59:** 1217–1232, 1948.

Davison, H. and Danielle, J. F.: The Permeability of Natural Membranes. Cambridge: at the University Press. New York: The Macmillan Company, 1943.

Ebert, C. E. and Bavetta, Lucien: 1.8 *per cent urea solution as isomotic fluid for trans*urethral prostatic resection. J. Urol., **60:** 933–936, 1948.

Ebert, C. E.: A clinical comparison of the use of glucose and urea in irrigating solutions for transurethral prostatic resections. J. Urol., **62:** 736–741, 1949.

Evans, C. L.: Starling's Principles of Human Physiology. Philadelphia: Lea & Febiger, 1941.

Flink, E. B.: Blood Transfusion, No. 3. J. Lab. and Clin. Med., **32:** 223, 1947.

Foy, H., Altmann, A., Bernes, H. D. and Kondi, A.: Anuria with special reference to *renal failure in black water fever*, incompatible transfusion reactions and crush injuries. Tr. Roy. Soc. Trop. Med. & Hg., **36:** 197, 1943.

Griffin, M.: Toxic symptoms accompanied by hemolysis during transurethral prostatectomy. J. Urol., **59:** 431, 1948.

Harrison, H. E., Bunting, H., Ordway, N. K. and Albrink, W. S.: The pathogenesis *of the renal injury produced in the dog by hemoglobin or methemoglobin.* J. Exp. Med., **86:** 339–356, 1947.

Hoffman, C. A. and Werthammer, S.: An unusual symptom complex following transurethral resections. J. Urol., **56:** 701–709, 1946.

Landsteiner, E. K. and Finch, C. A.: Hemoglobinemia accompanying transurethral resection of the prostate. New Eng. J. Med., **237:** 310–312, 1947.

Lucké, B.: Lower nephron nephrosis (the renal lesions of the crush syndrome of burns, transfusions, and other conditions affecting the lower segments of the nephrons). Military Surg., **99:** 371–396, 1946.

McLaughlin, W. L., Holyoke, J. B. and Bowler, J. P.: Oliguria following transurethal resection of the prostate gland. J. Urol., **58:** 47–60, 1947.

McLaughlin, W. L., Bowler, J. P. and Holyoke, J. B.: The causes of death following transurethral resection of the prostate. J. Urol., **59:** 1233–1238, 1948.

Maluf, N. S. R.: *Factors inducing renal shut-down from lysed erythrocytes:* An experimental study. Ann. Surg., **130:** 49–67, 1949.

Nesbit, R. M. and Glickman, S. I.: The use of glycine solution as an irrigating medium during transurethral resection. *J. Urol.*, **59:** *1212–1216, 1948.*

Ross, J. F.: Hemoglobinemia and the hemoglobinurias. New Eng. J. Med., **233:** 691, 732–766, 1945.

Selkurt, E. E.: The alteration of kidney circulation and function resulting from complete renal ischemia and hemorrhage shock. Am. J. Physiol., **145:** *699–709, 1946.*

Selkurt, E. E.: The changes in renal *clearance following complete* ischemia of the kidney. Am. J. Physiol., **144:** 395–403, 1945.

Trueta, J., Barclay, A. E., Daniel, P. H., Franklin, E. J. and Prichard, M. M. L.: Studies of the Renal Circulation. Nuffield Institute for Medical *Research, Oxford.* Blackwell Scientific Publications, Oxford. Toronto, Canada: Ryerson Press. Springfield, Ill.: Charles C Thomas 1948, 187 pp.

Woodruff, L. M. and Firminger, H. I.: Hemoglobinemia and hemoglobinuric nephrosis complicating transurethral resection of the prostate. J. Urol., **63:** 168–177, 1949.

Yuile, C. L., Gold, M. A and Hinds, E. G.: *Hemoglobin precipitation in* renal tubules. *A study of its causes and effects.* J. Exp. Med **82:** 361–374, 1945.

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HEMOGLOBINEMIA AND LOWER NEPHRON NEPHROSIS FOLLOWING TRANSURETHRAL PROSTATIC SURGERY

(The use of a new nonhemolytic irrigating solution, 3 per cent mannitol, as a preventive)

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Since the original observations of Wardill,[1] Creevy and Webb,[2] and McLaughlin et al.,[3] there has been a rapidly growing literature concerning the oliguria syndrome caused by renal damage following some cases of transurethral prostatic surgery.[4a–s]

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Hot Springs, Va., March 25, 1950.

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Most of the laboratory investigation described was done during 1947–48 when Dr. Goodwin was a National Research Council Fellow in the Medical Sciences.

The laboratory portion of the investigation was supported in part by a research grant from the National Institute of Health, Public Health Service.

[1] Wardill, W. E. M.: Benign enlargement of the prostate. (Medical Society of London discussion). Brit. J. Urol., 18: 72, 1946.

[2] Creevy, C. D. and Webb, E. A.: A fatal hemolytic reaction following transurethral resection of prostate gland: A discussion of its prevention and treatment. Surgery, 21: 56–66 1947.

[3] McLaughlin, W. L., Holyoke, J. B., and Bowler, J. P.: Oliguria following transurethral resection of the prostate gland. J. Urol., 58: 47–60, 1947.

[4a] Biorn, C. L. and Greene, L. F.: Hemolysis during transurethral prostatic resection. Surg., Gynec. & Obst., 88: 389–398, 1949.

[b] Bunge, R. G. and Barer, A.: Hemolysis during transurethral prostatic resection. J. Urol., 60: 122, 1948.

[c] Creevy, C. D.: Hemolytic reactions during transurethral prostatic resection. J. Urol., 58: 125–131, 1947.

[d] Creevy, C. D.: The importance of hemolysis during transurethral prostatic resection; a clinical investigation. J. Urol., 59: 1217–1232, 1948.

[e] Dees, T. A., Steward, W. D., Meares, E. F. and Orr, L. M.: Modified irrigating solution for transurethral prostatic resections: A preliminary report. J. Urol., 59: 212, 1948.

[f] Ebert, C. E. and Bavetta, L.: 1.8 per cent urea solution as isomotic fluid for transurethral prostatic resection. J. Urol., 60: 933–936, 1948.

[g] Ebert, C. E.: A clinical comparison of the use of glucose and urea in irrigating solutions for transurethral prostatic resections. J. Urol., 62: 736–741, 1949.

[h] Garske, G. L., Phares, O. C. and Sweetser, T. H.: The status of irrigating fluids for transurethral resection: our experience and a survey of the use of various solutions by others. J. Urol., 62: 322–327, 1949.

[i] Griffin, M.: Toxic symptoms accompanied by hemolysis during transurethral prostatectomy. J. Urol., 59: 431, 1948.

[j] Hemoglobinemia. *What's New*, p. 12, March 1948; Abbott Laboratories, North Chicago, Ill.

[k] King, K. B. and Werner, J. R.: Lower nephron nephrosis complicating transurethral resection: Some clinical observations. Trans. South Central Sect., AUA, pp. 83–88, 1947.

[l] Landsteiner, E. K. and Finch, C. A.: Hemoglobinemia accompanying transurethral resection of prostate. New Eng. J. Med., 237: 310–312, 1947.

[m] McLaughlin, W. L., Bowler, J. P. and Holyoke, J. B.: The causes of death following transurethral resection of the prostate. J. Urol., 59: 1233–1238, 1948.

[n] Nesbit, R. M. and Glickman, S. I.: The use of glycine solution as an irrigating medium during transurethral resection. J. Urol., 59: 1212–1216, 1948.

[o] O'Brien, H. A., Mitchell, J. D. and St. Martin, E. C.: Transurethral resection of large prostates. J. Urol., 63: 225–230, 1949.

[p] O'Brien, H. A. and Mitchell, J. D.: Hemolysis during transurethral resection. Trans. South Cent. Sect., AUA, pp. 89–92, 1947.

The kidneys of reported cases have uniformly shown hemoglobinuric[5] or "lower nephron"[6] nephrosis. (fig. 1). This renal lesion follows destruction of blood or tissue in a variety of conditions.[5,6,7] In nearly all cases in the urologic literature (excepting the first case reported by Creevy) shock, transfusion reaction, or sulfonamide intoxication may have contributed to the development of the syndrome in addition to postresection hemoglobinemia. Rich reviewed some deaths following transurethral resection and the oliguria syndrome in The Johns Hopkins Hospital and concluded that shock, transfusion reaction, or sulfonamide poisoning was the cause of the renal lesion in each case and doubted the importance or even the existence of hemoglobinemia caused by the resection.[8]

It has however been observed that hemoglobinemia occurs in 35 to 70 per cent of patients following prostatic resection when water is used as an irrigating solution.[4b,h,l,s] It has been demonstrated that irrigating fluid may enter the blood stream in amounts as great as 1000 cc,[4c] presumably by way of veins of the prostate and periprostatic plexuses. Hemoglobinemia is thought to result from intravascular hemolysis due to water or from escape of already hemolyzed blood from the operative field into the circulation.[2] No correlation has been observed between plasma hemoglobin levels and development of the oliguria syndrome following transurethral surgery. No cases have been reported where hemoglobin could *not* be demonstrated. In spite of many other possible contributory factors, the occurrence of free plasma hemoglobin directly attributable to transurethral resection has been held a suspect link in the chain of events leading to oliguria, uremia, and death following endoscopic surgery. It has been eliminated successfully by use of nonhemolytic irrigating solutions.[4–d,q]

CASE REPORTS

Two cases were selected from a review of several with like pathological findings because it seemed desirable in view of Rich's opinions and observations of others to rule out transfusions and sulfonamides as contributing factors.

Case 1. P. K. S. (J.H.H. U-65532), a 60 year old white man was hospitalized from October 17 to 19, and again from December 2 to 9, 1935, when he died in uremia 5 days after transurethral resection. The history was one of chronic, increasing prostatic obstruction. Examination revealed an otherwise healthy

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[q] Robbins, M. A., Olson, W. H. and Rolnick, H. C.: Clinical observations on use of a hemolytic and nonhemolytic irrigating medium for transurethral prostatic resection. Surgery, **27:** 254–259, 1950.

[r] Wear, J. B.: Some observations on technique of transurethral prostatic resection. J. Urol., **52:** 470–473, 1949.

[s] Woodruff, L. M. and Firminger, H. I.: Hemoglobinemia and hemoglobinuric nephrosis complicating transurethral resection of prostate. J. Urol., **62:** 168–177, 1949.

[5] Mallory, T. B.: *Hemoglobinuric nephrosis in traumatic shock.* Am. J. Clin. Path., **17:** 427–443, 1947.

[6] Lucké, B.: Lower nephron nephrosis (the renal lesions of the crush syndrome, burns, transfusions, and other conditions affecting lower segments of nephrone). Military Surg., **99:** 371–396, 1946.

[7] Strauss, M. B.: *Acute renal insufficiency due to lower nephron nephrosis.* New Eng. J. Med., **239:** 693–700, 761, 1948.

[8] Rich, A. R.: Clinical pathological conference, the Johns Hopkins Hospital, "Hemolysis from Water Irrigation during Prostatectomy as Cause of Renal Shut-Down." Jan. 3, 1949.

man with early prostatic hypertrophy Laboratory studies were normal: blood hemoglobin, 14 5 gm per cent, blood urea nitrogen, 24 mg per cent, phenolsulfonphthalein excretion, 78 per cent in 2 hours On December 4, 1935, 6¼ gm.

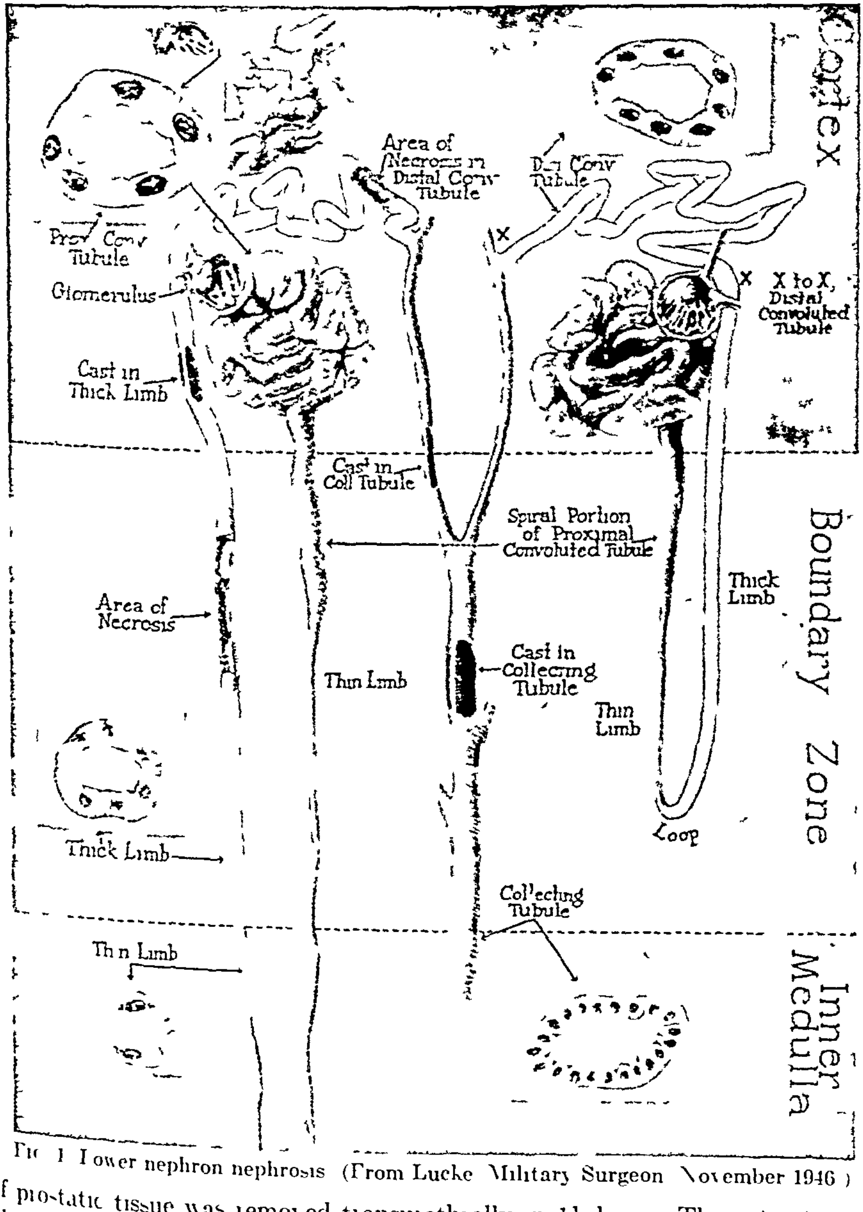

Fig 1 Lower nephron nephrosis (From Lucke Military Surgeon November 1946)

of prostatic tissue was removed transurethrally in 1¼ hours The patient complained of abdominal discomfort during the last part of the operation A hemostatic bag catheter was used at the end of the procedure He was never in shock He never received a transfusion or sulfonamides Progress notes described a sick patient with bloody catheter drainage and a painful abdomen. Extravasation was suspected. Postoperative oliguria and rise in blood urea nitrogen are shown in a graph (fig. 2). No jaundice was noted. A blood culture was sterile. On the fifth postoperative day left nephrostomy was done. The patient never responded and died shortly afterward.

Autopsy (No. 14549) was done the same day. The anatomical diagnosis was in part as follows: "Gangrene and infection of left anterior bladder wall. Extravasation of bloody urine about bladder extraperitoneally. Urethritis; cystitis; pyelitis and pyelonephritis. Blood pigment in renal tubules and renal epithelium. Hyalinization of rectus abdominis. Acute splenic tumor. Fat in liver. Hydrothorax, bilateral. Ascites. Hydrocele, bilateral. Oedema of testis. Ulcerative oesophagitis. Nephrostomy wound, lower pole of left kidney."

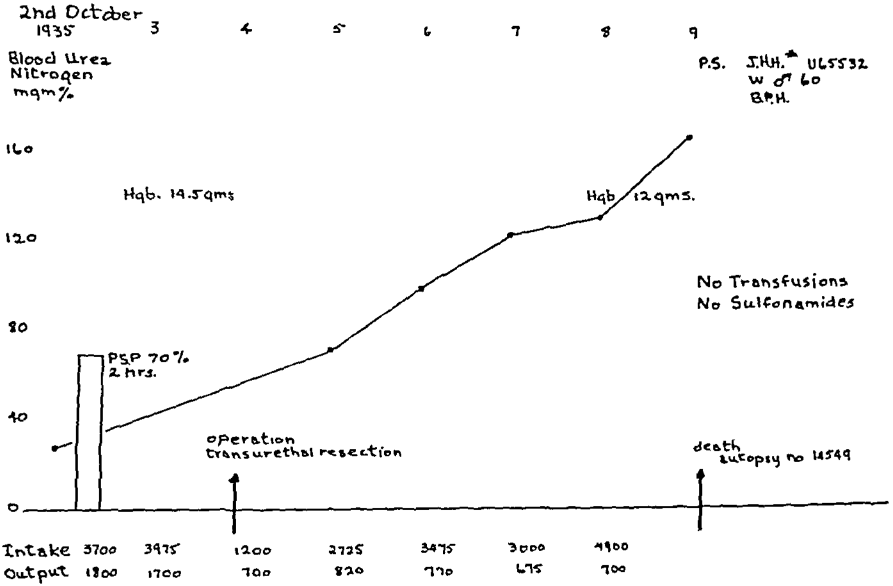

FIG. 2. Case 1. Clinical course showing rising blood urea nitrogen and oliguria.

Microscopic note about the kidneys (fig. 3) was as follows: "Glomeruli appear relatively normal save for an occasional fibrosed one. The lumen of most of the tubules is filled with a granular pink-staining coagulated fluid. The most conspicuous finding however, is the presence of coarse brown granular material in loops of Henle and distal convoluted and collecting tubules. Similar pigment is seen within the epithelial cells. *This pigment resembles that of transfusion reaction from mismatched blood, though there is no history of transfusion in this case.*"

Comment: Shock, transfusion reaction, and sulfonamide intoxication are ruled out by the history in this case. Undoubtedly perforation and extraperitoneal extravasation contributed to death. It is difficult to explain the renal lesions on this basis alone. He probably had post-resection hemoglobinemia and the "oliguria syndrome," which were unrecognized in those early days of resection.

Case 2. E. O. (J.H.H. No. 443,782) a 73 year old Negro, was admitted from November 25 to December 23, 1947. The symptoms were those of increasing prostatism. Examination revealed an otherwise healthy old man in acute urinary retention. He was catheterized and relieved suddenly of 750 cc of urine without obvious complication. Laboratory studies showed: blood hemoglobin 14.5 gm. per cent; blood nonprotein nitrogen, 40 mg. per cent. No phenolsulfonphthalein test was done. Urine specific gravity was 1.020. There was "2+" albuminuria. On November 27, an assistant resident performed transurethral resection of 20 gm. of prostatic adenoma in 1½ hours. Anesthesia was spinal pontocaine. The operative note is interesting: "The patient did well up to this point. [The last 30 minute period.] The operator suddenly noticed a great amount of bleeding, which was impossible to control. It had been dry previously but was now oozing from all parts of the prostatic fossa. There appeared to be hemoglobinuria from both ureteral orifices. Blood pressure was reported by the anesthetist as 290/160 mm. of mercury." The patient's blood plasma at this time was found to contain 875 mg. per cent free hemoglobin (fig. 4). He never showed signs of shock and never received a blood transfusion or sulfonamides, but he was extremely restless and uncooperative. He developed anemia, oliguria and progressive uremia postoperatively (fig. 5). He nearly died but slowly recovered and was discharged on the twenty-sixth postoperative day with still elevated blood nonprotein nitrogen.

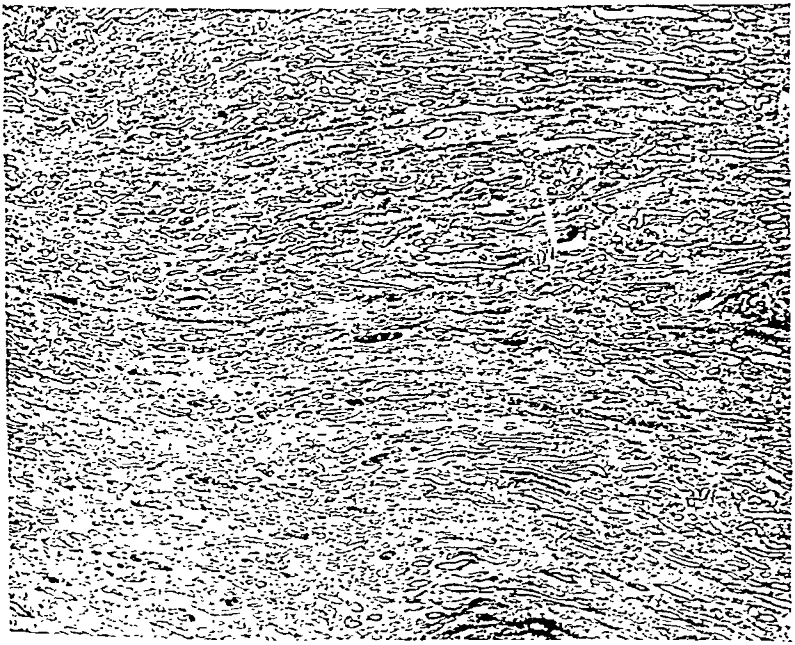

FIG. 3. Case 1. Kidney showing heme casts. × 25

Comment: The patient had clinical lower nephron nephrosis which was not fatal. He never suffered shock, and he was never given sulfonamides or transfusions. He had a high plasma hemoglobin level (the highest we have measured in these cases) after transurethral prostatic resection. Water was the irrigating fluid. The cause of the severe hypertensive episode during resection is not clear.* Others have commented on like episodes.[3,4–8]

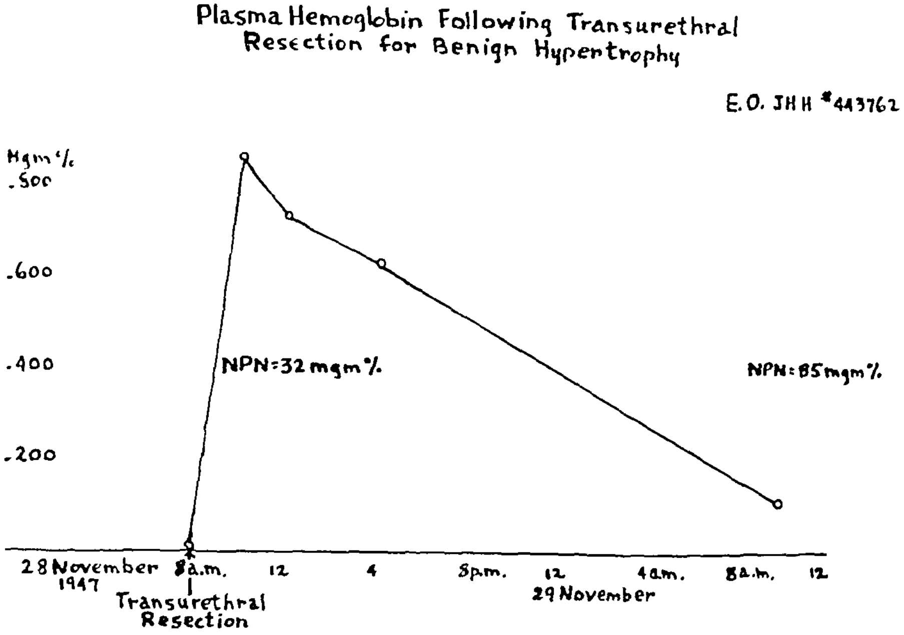

FIG. 4. Case 2. Postoperative blood levels of plasma hemoglobin (875 mg. per cent immediately postoperatively, 120 mg. per cent the next morning).

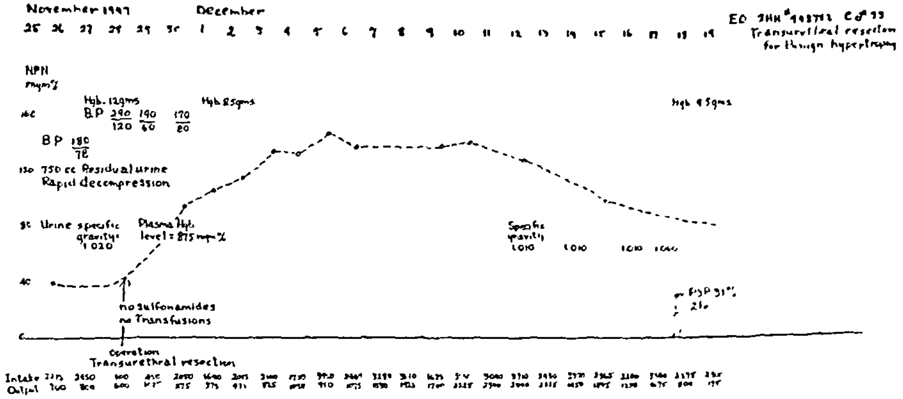

FIG. 5. Case 2. Clinical course showing oliguria, fixed specific gravity, anemia and rise in blood nonprotein nitrogen.

LABORATORY EXPERIMENTS

1. Increased red blood cell fragility after prolonged fulguration and excessive heat, as a possible source of hemoglobinemia Shen and Ham found hemoglobinemia and hemoglobinuria before death from severe burns and uremia in victims of the Cocoanut Grove disaster.[9] They tested osmotic fragility of red blood cells in these patients and found it was increased. This was equated with exposure to extreme heat which had been shown experimentally to produce hemolysis. The hemoglobinuric renal lesion was found in these cases and has since been described by others.[10,11]

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* Dr. Ralph Landes has suggested that this may be due to the sudden large increase in blood volume caused by entrance of irrigation fluid into the circulation.

[9] Shen, S. C., Ham, T. H. and Fleming, E. M.: Studies in destruction of red blood cells

The possibility that local burning during resection might produce hemolysis was considered as a possible source of hemoglobinemia following transurethral surgery. This was tested in 24 patients. Blood was drawn before and after resection and studied for osmotic fragility of red blood cells using the method of Shen and Ham.[9]

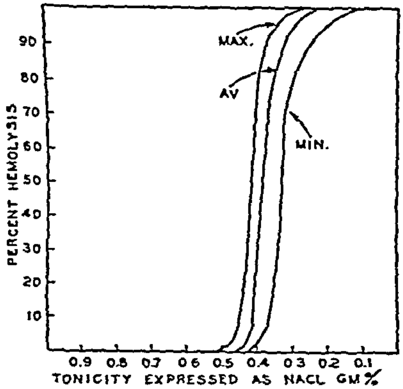

FIG. 6. Normal osmotic fragility curves. (After Shen and Ham, New Eng. J. Med., Nov. 1943.) (The 24 cases studied in this series never fell outside these curves even after resection.)

About a third of the cases showed hemolysis in some degree postoperatively. Although there were detectable shifts toward increased fragility in postoperative blood samples compared to preoperative ones, none showed increased fragility beyond the range of normal (fig. 6). It was concluded that hemolysis, when it occurred, was not related to increased fragility of red blood cells in these cases.

2. *Methemoglobin production during transurethral resection.* Theoretically, hemoglobin liberated from red blood cells within the bladder could be converted to methemoglobin by the heat of resection. Experiments with heme pigments in dogs have suggested that methemoglobin is more nephrotoxic than other pigments.[12] This has been challenged,[13,14] but the problem exists whenever renal damage associated with hemoglobinemia is considered.

III. Mechanism and complications of hemoglobinuria in patients with thermal burns: Spherocytosis and increased osmotic fragility of red blood cells. New Eng. J. Med., 229: 701–713, 1943.

[10] Goodpastor, W. E., Levenson, S. M. Tagnon, H. L., Lund, C. C. and Taylor, F. H. L.: A clinical and pathologic study of the kidney in patients with thermal burns. Surg., Gynec. & Obst., 82: 652, 1946.

[11] Martineau, P. C. and Hartman, F. W.: The renal lesions in extensive cutaneous burns. J. A. M. A., 134: 429, 1947.

[12] Bing, R. J.: The effect of hemoglobin and related pigments on renal functions of normal and acidotic dogs. Bull. Johns Hopkins Hosp., 74: 161, 1944.

[13] Hamilton, P. B., Hiller, A. and Van Slyke, D. D.: Renal effects of hemoglobin infusions in dogs in hemorrhagic shock. J. Exp. Med., 86: 477–487, 1947.

[14] Harrison, H. E., Bunting, H., Ordway, N. K. and Albrink, W. S.: The pathogenesis of renal injury produced in the dog by hemoglobin or methemoglobin. J. Exp. Med., 86: 339–356, 1947.

The plasma of two patients having post resection levels of 150 mg. per cent was tested for methemoglobin. In two other experiments, bloody irrigating fluid was tested for methemoglobin after prolonged fulguration.

The Beckman spectrophotometer was used. Results were compared with standard curves for oxyhemoglobin and methemoglobin.[15–a,b,c]

In each case curves were almost identical with the standard for pure hemoglobin (fig. 7). Patients on whom these studies were made did not develop signs of renal insufficiency. It can be concluded from this evidence, only that methemoglobin was not present under these conditions. It would be important further to study the problem and to determine the nature of the plasma pigment in a case that subsequently *did* develop the oliguria syndrome after transurethral resection.

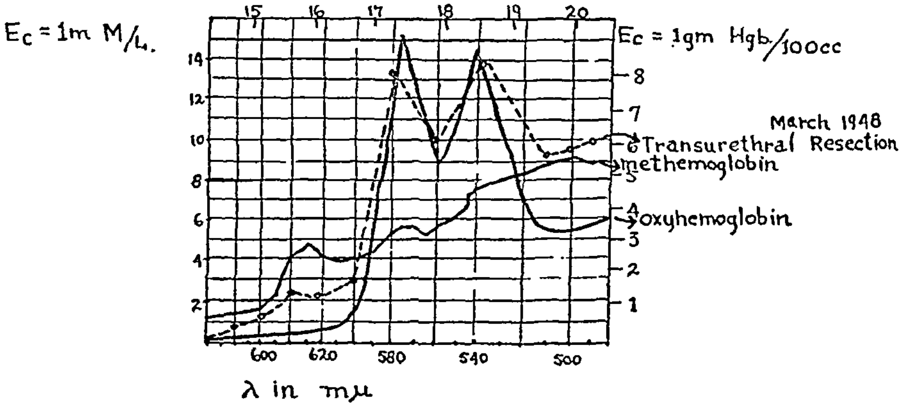

FIG. 7. Spectrophotometer curves: Oxyhemoglobin, methemoglobin, and plasma hemoglobin = dotted line (from patient with hemoglobinemia following transurethral resection).

3. Bacteremia caused by the resection. Since in some cases the irrigating fluid enters the blood stream, it may carry bacteria or other toxic products along with it.[2,3] In 6 cases blood cultures were made immediately after transurethral surgery. All were sterile. We recall other cases where shaking chills were noted postoperatively. Since then a thorough study of this problem has been made by Biorn et al.[16] They found that 12.2 per cent of 106 cases developed transient bacteremia after resection at the Mayo Clinic. None developed septicemia. The clinical significance, if any, was not conclusive. None of their patients and none of the 6 cases in our series developed renal insufficiency. It would be important to have blood culture studies on a group of patients who *did* develop the oliguria syndrome.

[15-a] Austin, J. H. and Drabkin, D. L. Spectrophotometric studies: "Methemoglobin." J. Biol. Chem., 112: 67, 1935.

[b] Austin, J. H. and Drabkin, D. L.: Preparations from washed blood cells; nitric oxide hemoglobin and sulfhemoglobin. Ibid. p. 51.

[c] Drabkin, D. L. and Austin, J. H.: Spectrophotometric studies V. A technique for analysis of undiluted blood and concentrated hemoglobin solutions. J. Biol. Chem., 112: 105–115, 1935.

[16] Biorn, C. L., Browning, W. H. and Thompson, L.: Transient bacteremia immediately following transurethral prostatic resection. J. Urol., 63: 155–161, 1950.

INCIDENCE AND EXTENT OF HEMOGLOBINEMIA FOLLOWING TRANSURETHRAL PROSTATIC RESECTION WITH WATER AS AN IRRIGATING MEDIUM

The frequency of post-resection hemoglobinemia is estimated at 35 to 70 per cent depending on the criteria.[4b,h,l,s] The most complete study is by Bunge and Barer. Our results are compared with theirs in table 1.

TABLE 1. *Incidence of hemolysis in transurethral resection with water as the irrigating fluid*

PLASMA HGB MG. %	THIS STUDY 69 CASES	BUNGE AND BARER 100 CASES
Group I less than 50 mg.%	"no visible hemolysis" 45 cases 65%	64 cases (64%)
Group II 51 to 100 mg.%	total—7 cases (10%) 5 cases, "1+" hemolysis 1 case, 75 mg.% 1 case, 100 mg.%	19 cases (19%)
Group III 101 mg.% and above	total—17 cases (25%) 118 mg.% 135 150 (Clinical L.N.N., Death) 166 187 195 226 238 264 300(Clinical L.N.N., Death) 310 376 (Clinical L.N.N., Survival) 400 (Clinical L.N.N., Survival) 400 660 660 875 (Clinical L.N.N., Survival) (E.O.)	17 cases (17%)
	Total Cases in Groups II and III	
	24 cases (35%)	36 cases (36%)

From August 1947 to December 1948, occurrence of plasma hemoglobin was studied in 69 unselected cases (about $\frac{1}{3}$ of all resections) after transurethral surgery when water was the irrigating medium.

Methods. Venous blood was drawn after resection through a No. 18 needle into a syringe wet with normal saline. Four cc of blood were gently expressed into a graduated centrifuge tube containing 1 cc of anticoagulant citrate solution and centrifuged for 10 minutes. The supernatant mixture of plasma and citrate was examined for hemoglobin by the photoelectric method of Evelyn and Malloy.[17] Controls never gave false positive evidence of hemolysis.

Results. The results are shown in table 1. Plasma hemoglobin levels below 50 mg. per cent were not considered significant. If this same dividing line is used in the cases reported by Bunge and Barer, a close correlation in results between their series and ours is seen.

INCIDENCE OF THE OLIGURIA SYNDROME

The oliguria syndrome developed 5 times in 24 cases showing hemolysis. It was recognized clinically by azotemia, oliguria, and fixed specific gravity of urine. Two of five patients in whom it developed, died; in each case autopsy showed that the kidneys contained lesions of lower nephron nephrosis. These cases are not reported in detail because they had transfusions which may have been a factor, but no transfusion reactions were noted. The two patients who died had plasma hemoglobin levels of 300 and 150 mg. per cent, respectively. The 3 who survived after developing the syndrome clinically had levels of 875 mg. per cent (case No. 2, above) 400 mg. per cent and 376 mg. per cent after resection.

Other patients with high plasma hemoglobin levels never developed evidence of renal insufficiency. There was no apparent correlation between the amount of hemolysis and the degree of subsequent renal insufficiency, except that in all cases in which the oliguria syndrome developed, the patients exhibited hemoglobinemia and were in group 3 (i.e., plasma hemoglobin levels over 100 mg. per cent. In Bunge's series of 100 cases, 3 developed signs of renal insufficiency, and 1 died.

Some degree of hemoglobinemia follows transurethral resection when water is used as the irrigating medium, in about *one out of every three cases.* Of cases showing hemoglobinemia, between 10 and 20 per cent develop the oliguria syndrome. Seriousness of the reaction and ultimate outcome may depend more on other factors than on the amount of hemoglobin, although hemoglobinemia has been incriminated as a contributory factor in each case.

THE PREVENTION OF HEMOGLOBINEMIA AFTER RESECTION

Although many other factors than hemoglobinemia are known to exist, several workers have focused attention on use of nonhemolytic irrigating solutions in an attempt to prevent the post-resection oliguria syndrome and to lessen dangers of extravasation. The use of glucose as an irrigating medium was first suggested by Ebert. Creevy and others have written of their experiences with this and agreed that search for an even better solution is in order. Nesbit and Glickman have used glycine. Ebert and Bavetta have described the use of urea to minimize dangers of extravasation.

An "ideal" irrigating solution should be a nonelectrolyte and nonhemolytic. It should be nonmetabolized and yet nontoxic. It would preferably be a diuretic.

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[17] Evelyn, K. A. and Malloy, H. T.: *Microdetermination of oxyhemoglobin, methemoglobin, and sulfhemoglobin in a single sample of blood.* J. Biol. Chem., 126: 655, 1938.

It should be physically almost identical with water as concerns touch, appearance, clearness, and refractive index. It should be readily available and inexpensive. It should be subject to easy sterilization and storage. It should give clear visibility at all times during resection. Dr. Eliot Newman of the Department of Medicine suggested mannitol as the substance most likely to fulfill those criteria.

MANNITOL

Mannitol[18] (fig. 8), $C_6H_{11}O_6$, a crystalline powder, is a hexahydric sugar alcohol naturally occurring in the manna ash. It is the main ingredient of commercial manna which is known for its sweetness and mild laxative action. Together with its isomer, sorbitol, it has been used as a substitute for sugar in diabetic diets for more than a decade. It is readily soluble in hot water and forms a neutral solution. It is heat stable and chemically stable in its dry powder or sterile aqueous solutions. In the body, 85 to 90 per cent of it is excreted unchanged in the urine in 10 hours. Its injection does not significantly effect blood glucose, and it is in the same clase as glucose or sucrose as regards toxicity.[19a,b] It is excreted chiefly by the glomeruli and acts as an effective osmotic diuretic. (On occasion we have used it or glucose intravenously in 12½ per cent solution to produce diuresis during ureteral catheterization.) It has been used in large doses intravenously to determine renal function as its excretion is a good measure of glomerular filtration rate.[20] It is a byproduct of gunpowder manufacture and is thus, in these days, plentiful. It is available in two grades, "reagent grade" in 50 pound containers at 85 cents per pound, and a slightly less pure "commercial grade" in 150 pound containers at 43 cents per pound.

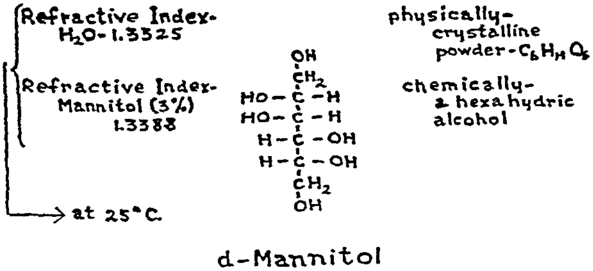

FIG. 8. Formula and physical characteristics of Mannitol.

EXPERIENCES WITH MANNITOL SOLUTIONS AS AN IRRIGATING MEDIUM IN TRANSURETHRAL RESECTION

We have used "reagent grade" mannitol, but difference in specifications of the two grades is so slight that there is probably no good reason why the less expensive product should not be used. To determine the minimal effective per cent solution that would not be hemolytic, an osmotic fragility test was made with mannitol solutions varying in strength from ½ to 10 per cent. There was a slight change with the 2 per cent solution and frank hemolysis with the 1½ per cent solution. It was apparent that a 3 per cent solution would be adequate to prevent hemolysis. A 3 per cent solution was chosen.

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[18] Supplied through courtesy of Mr. N. P. Spang, Atlas Powder Co., Wilmington, Del.

[19a] Atlas Powder Co., Wilmington 99, Del.: Brochure on mannitol; personal communication.

[b] Ellis, F. W. and Krantz, J. C.: Sugar alcohols XXII. Metabolism and toxicity studies with mannitol and sorbitol in man and animals. J. Biol. Chem., 141: 147–154, 1941.

[20] Smith, W. W., Finkelstein, N. and Smith, H. W.: Renal excretion of hexitols (sorbitol, mannitol and dulcitol) and their derivatives (sorbitan, isomannide and sorbide) and of endogenous creatinine-like chromogen in dog and man. J. Biol. Chem., 135: 231–250, 1940.

In this concentration mannitol solutions are indistinguishable from water in appearance, consistency on gloves, and visibility at cystoscopy. The only complaints have been those concerning decreased visibility during severe bleeding when the lack of hemolysis hampers the operator unaccustomed to nonhemolytic solutions. This has caused some members of the staff to reject the solution after one or two trials. Others after a longer trial or after an unfortunate experience with the oliguria syndrome have become used to it. Those who use it exclusively have learned to experience no more difficulty in vision than with water. Impaired visibility in the presence of severe bleeding is common with all nonhemolytic solutions.

In the operating room two irrigating flasks, one containing water and the other 3 per cent mannitol solution, are available. Occasionally, an operator will do most of a resection using mannitol, changing to water at the end of the procedure. This seems to produce as satisfactory results as use of mannitol alone.

Preparation of solutions. The pharmacy has prepared solutions which are autoclaved as in preparation of glucose for intravenous use. If this service were not available, it would be useful to have mannitol in concentrated sterile solutions, which could easily be diluted to proper percentage with water.

Results. Three per cent mannitol solution has been used as an irrigating medium in approximately 250 transurethral resections since August 1947. In 36 cases blood plasma was examined postoperatively for hemolysis. In an additional eight cases mannitol solution was used during the first part of resection and water during the latter part (table 2). *None of these cases showed hemolysis. None* of the cases without hemolysis *showed recognized evidence of the oliguria syndrome.* If results of the parallel series of resections with water are indicative, hemolysis should have occurred once or more in every three resections. Known extravasation occurred twice and suspected extravasation occurred twice when mannitol was in use. Although these patients developed some abdominal rigidity and pain, none of them developed shock or suffered any identifiable later after effects. None of them showed the oliguria syndrome.

Previous evidence for escape of irrigating fluid into the blood stream is convincing.[4–1] We have not examined blood for evidence of mannitol after resection when it was used. No toxic effects have been observed. This study and reports of others indicate that use of nonhemolytic irrigating solutions in transurethral surgery has eliminated the occurrence of hemoglobinemia postoperatively. There is some evidence to indicate that these solutions lessen the hazardous complications of extravasation.

Mannitol, in 3 per cent solution, has proven very satisfactory in transurethral resections reported in this study. It possesses certain advantages over glu-

TABLE 2. *Transurethral resections with postoperative measurement of plasma hemoglobin*

FLUID	WATER	MANNITOL	MANNITOL AND WATER
Total number of cases	69	36	8
Cases showing hemolysis	24 (34.8%) plasma hemoglobin levels 75–875 mg. %	0	0
Clinical lower nephron nephrosis	5 (20% of hemolysis cases 7.2% of all cases)	0	0
Deaths with lower nephron nephrosis	2 1 extravasation 1 no extravasation	0	0

TABLE 3. *Comparison of various irrigating solutions used in transurethral resections*

INVESTIGATOR	SUBSTANCE	% SOLUTION	PROPERTIES	NUMBER OF RESECTIONS	WILL CONTINUE USE	COST
EBERT	urea	1.8	hemolytic iso-osmotic normal constituent	300–350	yes	75–85/lb.
CREEVY	glucose	4.0	nonhemolytic non toxic normal constituent sticky	1000+	yes	.26/lb.
NESBIT	glycine	2.1 1.1	nonhemolytic non toxic not sticky	500 (approximately)	yes	.40/gal. $2.00/lb. (approximately)
THIS STUDY	mannitol	3.0	nonhemolytic not metabolized diuretic nontoxic like alcohol	250 (approximately)	yes	.85/lb. reagent grade .43/lb. commercial grade

cose and glycine (table 3). It is not sticky. It has nearly the same refractive index as water. It has no effect on diabetics. It is cheaper than glycine. The fact that it is nonhemolytic makes it superior to urea. The osmotic diuretic effect of mannitol may represent another advantage. Renal tubular damage after shock or associated with hemoglobinuria may be related to formation of obstructing casts during oliguria. Selkurt has shown in dogs that infusions of mannitol partially "protect" the kidneys from decrease in function following renal ischaemia.[21a,b] He states: "Because the osmotic diuretic, mannitol, improves urine flow and clearances when used after renal ischaemia, the suggestion follows that the use of this diuretic or one having similar properties, might prove helpful in treating the cases of persistent renal failure and uremia which are seen following certain cases of shock, when blood pressure and renal circulation have been restored by infusion of plasma or blood."

This sugar alcohol, the chief constituent of manna, may be nearly an "ideal" irrigating medium. If other work on nonhemolytic solutions and our own experiences are fair samples, the use of mannitol gives good promise of decreasing complications following transurethral resection of the prostate gland.

DISCUSSION

Hemoglobinemia occurs after transurethral resection in more than a third of cases when water is used as an irrigating medium. The fact that the oliguria syndrome occurs much less commonly raises important questions: When, if ever, does hemoglobinemia contribute to renal insufficiency? Is it ever a factor in cases of post-resection oliguria syndrome? Maximum plasmae hmoglobin levels (less than 1000 mg. per cent) so far observed after resection are not sufficiently high to produce lasting renal damage due to hemoglobin alone in animals or man.[22a,b,c,d,e,f.] It is necessary then to adduce other factors which may act singly or together to produce renal insufficiency and which when present in conjunction with hemoglobinemia may predispose to development of lower nephron nephrosis. It is unlikely that the exact importance of each factor or combinations of them can be completely understood in every case developing the oliguria syndrome after resection. It is important to consider them separately and to try to eliminate or minimize them in standardizing techniques for endoscopic prostatic surgery. Most possible factors have been described:[3,4c]

Hemoglobinemia. Renal insufficiency produced by hemoglobinemia in dogs is proportional to hemoglobin concentration. Critical levels are not reached until concentrations approach 3700 mg. per cent.[22a,b] Pre-existing renal damage from ischemia or nephrotoxic agents makes kidneys more sensitive to hemoglobin

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[21-a] Selkurt, E. E.: The changes in renal clearance following complete ischemia of the kidney. Am. J. Physiol., 144: 395–403, 1945.

[b] Selkurt, E. E.: The alteration of kidney circulation and function resulting from complete renal ischemia and hemorrhagic shock. Am. J. Physiol., 145: 699–709, 1946.

[22-a] Flink, E. B.: Blood transfusion No. 3. J. Lab. & Clin. Med., 32: 223, 1947.

[b] Flink, E. B.: Certain aspects of hemoglobinemia. Its relation to renal damage in dogs and its diagnostic significance in transfusion reactions. (A thesis submitted to the graduate faculty of the University of Minnesota.) 1945.

[c] Gilligan, D. R., Altschule, M. D. and Katersky, E. M.: Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions. J. Clin. Investigation, 20: 177, 1941.

[d] Monke, V. J. and Yuile, C. L.: The renal clearance of hemoglobin in the dog. J. Exp. Med., 72: 149–165, 1940.

[e] Stats, D., Wasserman, L. R. and Rosenthal, N.: Hemolytic anemia with hemoglobinuria. Am. J. Clin. Path., 18: 757, 1948.

[f] Yuile, C. L.: Hemoglobinuria. Physiological Rev., 22: 19–31, 1942.

damage.[23] Dogs treated with hemoglobin as a blood substitute during hemorrhagic shock, showed depression of urea clearances lasting 5–6 days.[15] Control dogs with shock alone showed transitory depressed renal function but returned to normal the next day. It was concluded: there was sufficient possibility of renal damage by hemoglobin solution to prevent its use.

These observations are adequate reason for eliminating hemoglobinemia due to resection. Use of nonhemolytic solutions has accomplished this.[4d,h,n,s] Several authors have indicated satisfaction with isotonic solutions. They intend to continue using them until something better is available.[4d,l,n,o,p]

Shock; tissue damage; heat. Shock alone or with other factors may produce irreversible renal damage.[5, 6, 24a,b] Effects of tissue damage (usually associated with shock) are described in relation to trauma.[25a,b] Specific effects of prostatic tissue damage and deep fulguration of the prostate are not known. It may add to renal damage as do traumatic injuries elsewhere in the body. The effect of heat on blood has been observed in the present study. It does not seem to be a factor. Shock should be controlled by adequate intravenous fluids and blood. Excessive tissue damage is minimized by careful point fulguration with proper currents.

Perforation; extravasation. The exact importance of extravasation without other factors is not known.[25] It may produce severe tissue damage. Yet there have been cases suffering little more than transient discomfort. Minor perforations and extravasation may be dealt with by watchful waiting. Any large amount of extravasated fluid or any large perforation which may later drain urine should be treated surgically as soon as recognized. Use of isotonic irrigating solutions minimizes the damage and dangers of these accidents.

Hepato-renal syndrome. Renal and liver damage is described after prolonged and traumatic operative procedures.[27a,b] Several cases in the literature of oliguria syndrome after resection have shown liver damage. It was present in case 1 of our study. Whether liver or renal damage comes first is not known. It has been attributed to general damage produced by shock and tissue destruction. Estimation of preoperative liver function may be indicated in poor risk cases. Limiting resection to one hour and attention to other factors mentioned here should help to eliminate this complication.

Transfusion reactions. Transfusion reactions are a common cause of lower nephron nephrosis.[6, 22a, 28] Possibility of this complication exists in nearly every case of post-resection oliguria syndrome described. The 2 cases presented here did not have transfusions. Care in blood matching and transfusion reduces accidents but is not infallible.

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[23] Yuile, C. L., Gold, M. A. and Hinds, E. G.: Hemoglobin precipitation in renal tubules. A study of its causes and effects. J. Exp. Med., 82: 361–374, 1945.

[24a] Phillips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K., Archibald, R. M. and Van Slyke, D. D.: Effects of acute hemorrhagic and traumatic shock on renal functions of dogs. Am. J. Physiol., 145: 314–336, 1946.

[5] Van Slyke, D. D.: The effects of shock on the kidney. Ann. Int. Med., 28: 701–722, 1948.

[25a] Corcoran, A. C. and Page, I. H.: Post-traumatic renal injury, summary of experimental observations. Arch. Surg., 51: 93–101, 1945.

[25b] Corcoran, A. C. and Page, I. H.: Crush syndrome: Post-traumatic anuria: Observations on genesis and treatment. J. A. M. A., 134: 436–441, 1947.

[26] Hoffman, C. A. and Werthammer, S.: An unusual symptom complex following transurethral resections. J. Urol., 56: 704–709, 1946.

[27a] Boyce, F. F. and McFettridge, E. M.: The so-called "liver death." Arch. Surg., 32: 1080, 1936.

[27b] Garlock, J. K. and Klein, J. H.: So-called hepatorenal syndrome. Ann Surg., 107: 82, 1938.

Sulfonamide toxicity. Sulfonamides alone can cause lower nephron nephrosis.[6] They should never be given to a patient who is suspected of having the oliguria syndrome. Perhaps since streptomycin and penicillin are available, use of sulfonamides should be given up in immediate pre- and postoperative care of patients undergoing resection.

Pituitary antidiuretic hormone. It is known that pituitary antidiuretic hormone produces oliguria after painful stimuli.[29] If this occurs during resection, it is probably transitory. Osmotic diuretic effects of hypertonic glucose or mannitol solutions may combat it.

Methemoglobin. Though evidence is contradictory, methemoglobin may be more nephrotoxic than hemoglobin.[12] If it ever exists due to resection, it may be prevented by use of nonhemolytic solutions.

Nephrotoxic substances liberated by extravasating fluid. This is an unknown quantity as far as experimental work is concerned. If it is a factor, diuresis should help protect the kidneys.

State of dehydration. Renal insufficiency due to hemoglobin develops at much lower levels of hemoglobinemia during severe dehydration.[30] Mechanical blocking of renal tubules with casts of hemoglobin during oliguria or anuria may explain this. Patients awaiting resection should take fluids by mouth until 4–6 hours before operation. Intravenous glucose infusions should be used during and after resection.[31]

Bacteremia caused by resection. Transient bacteremia may occur in about 12% of the cases without lasting effect.[16] We recall a case where irrigating fluid could be seen entering the vessels, and septicemia developed. Antibiotics pre- and postoperatively should minimize dangers from such accidents.

Acidosis. There is conflicting evidence concerning the role of acidosis in development of renal insufficiency due to hemoglobin.[22b, 24a, 30, 32] It is sensible to make sure that the patient is not acidotic before resection and does not develop acidosis postoperatively. Hemorrhagic shock produces acidosis. It is probably wise to give alkalinizing solutions before transfusion during shock. Judicious use of lactate solutions is not harmful and may be helpful.

Pre-existing renal damage. Ischemia or injection of nephrotoxic sodium tar-

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[28] DeGowin, E. L., Warner, E. D. and Randall, W. L.: Renal insufficiency from blood transfusion. "II. Anatomical changes in man compared with those in dogs with experimental hemoglobinuria." Arch. Int. Med., 61: 609, 1938.

[29] O'Connor, W. J. and Verney, E. B.: The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. Quart. J. Exper. Physiol., 33: 77, 1946.

[30] Maluf, N. S. R.: Factors inducing renal shut-down from lysed erythrocytes: An experimental study. Ann. Surg., 130: 49–67, 1949.

[31] Olson, W. H. and Necheles, H.: Use of parenteral fluids in hemoglobinuric nephrosis. Am. J. Physiol. (Proceedings), 163: 739, 1950.

[32] DeGowin, E. L., Osterhagen, H. F. and Andersch, M.: Renal insufficiency from blood transfusion. "I. Relation to urinary acidity." Arch. Int. Med., 59: 432, 1937.

trate predisposes to worse renal damage from subsequent injections of relatively small amounts of hemoglobin.[23] In our own experience some dogs with previously hydronephrotic kidneys developed more severe renal insufficiency after sublethal doses of intravenous hemoglobin than normal dogs. Old dogs did not tolerate such experiments as well as young ones. The same is probably true in humans. It is important to study renal function before transurethral surgery. Blood nonprotein nitrogen and CO_2 estimations as well as phenolsulfonphthalein tests, specific gravity studies, and excretory urograms should be part of the complete preoperative study.

Renal ischemia due to shock; due to neurovascular effects. Renal ischemia reduces renal function.[21a,b 24b, 33] This leads to more severe damage from hemoglobin.[23] Severe shock produces renal ischemia. The possibility of an added neurovascular effect related to resection has to be considered. Stimulation of splanchnic and renal nerves produces renal ischemia.[34a,b] Trueta further showed a similar effect by sciatic nerve stimulation, presumably acting by sympathetic reflex arc to the renal nerves.[35] Possibly prolonged electrocoagulation (sometimes associated with kicking of the legs as evidence of nerve stimulation) may act to produce such a stimulus. Extravasating fluid might also produce it.

Osmotic diuretics may act to protect renal function in the post-ischemic state.[21a,b] Renal ischemia should be prevented by avoiding shock and prolonged and deep fulguration.

Duration of the resection. That prolonged resection may prove dangerous seemed true in our cursory review of transurethral deaths in this hospital. Most fatal complications occurred when long and bloody resections were carried out by beginners. As Nesbit and others have indicated, resecting time should be limited to one hour. Prolonged major surgery reduces renal function.[36]

Uretero-renal reflux. Reflux of irrigating fluid via nonfunctioning ureterovesical valves may occur. We recall a case with bilateral reflux demonstrated by cystogram preoperatively, who experienced severe flank pain, nausea and vomiting during resection. Known reflux may be a contra-indication to transurethral surgery. If resection is unavoidable, small amounts of irrigating fluid under low pressure should be used.[37]

Postoperative irrigations. Postoperative irrigations may enter the blood stream.[4r] Sterile, isotonic solutions should be used in small quantities if necessary. It is better not to use irrigations postoperatively if they can be avoided.

[33] Koletsky, S. and Gustafson, G. E.: The effects of temporary cessation of renal blood flow in rats. J. Clin. Investig., 26: 1072–1078, 1948.

[34-a] Trueta, J., Barclay, A. E., Daniel, P. H., Franklin, E. J. and Prichard, M. M. L.: Studies of the renal circulation. Huffield Institute for Medical Research, Oxford. Oxford Blackwell Scientific Publications. Toronto, Canada: Ryerson Press. Springfield, Ill. Charles C. Thomas, 1948, 187 pp.

[b] Goodwin, W. E., Sloan, R. D. and Scott, W. W.: The Trueta renal vascular "shunt." J. Urol., 61: 1010–1027, 1949.

[35] Goodwin, W. E., Harris, A. P. and Scott, W. W.: Effects of peripheral stimuli on divided renal function. Am. J. Physiol. (Proceedings), 163: 715, 1950.

[36] Moyer, C. A.: Acute temporary changes in renal function associated with major surgical procedures. Surgery, 27: 198–207, 1950.

[37] Creevy recommends preoperative trocar cystostomy in these cases.

Experience of the resectionist. This is probably the most important and unpredictable factor of all. Even the most experienced transurethral surgeons have occasional difficulties. These are amplified when operation is in the hands of a neophyte or the occasional and inexperienced operator. In this single element all those previously mentioned are compounded. There are some resectionists in this clinic who have never had a death from post-resection oliguria syndrome. The most spectacular and serious complications have occurred during operations being performed by those just learning the procedure.

SUMMARY AND CONCLUSIONS

The oliguria syndrome and lower nephron nephrosis following some cases of transurethral prostatic surgery are discussed in relation to hemoglobinemia and other factors caused by resection.

Two cases of the oliguria syndrome, selected because blood transfusion and sulfonamide reactions could be ruled out as contributing factors, are presented and discussed.

Laboratory studies of some factors causing hemoglobinemia or renal damage are described:

1. Increased fragility of red blood cells due to heat is ruled out as a factor.
2. Methemoglobin production during transurethral resection is probably ruled out.
3. The role of bacteremia caused by resection is minimized.

Hemoglobinemia over 50 mg. per cent occurred 24 times in 69 cases studied after transurethral surgery when water was the irrigating medium.

Use of nonhemolytic solutions to prevent post-resection hemoglobinemia is discussed. Three per cent mannitol is suggested as a new medium for this purpose. Satisfactory use of this solution in approximately 250 transurethral resections since August 1947 is reported. Although expected incidence of hemoglobinemia after prostatic resection when water is the irrigating medium is 35 per cent, no hemoglobinemia was observed in 36 cases studied when mannitol was the irrigating fluid or in an additional 8 cases when mannitol followed by water at the end of resection was employed.

Use of nonhemolytic irrigating solutions is justified and desirable. Three per cent mannitol is satisfactory for this purpose and may be superior to glucose, glycine, and urea.

Eighteen factors which may singly or in combination contribute to lower nephron nephrosis and post-resection oliguria syndrome are discussed. Suggestions are made for eliminating or minimizing them.

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EVALUATION OF HORMONAL THERAPY FOLLOWED BY RADICAL PERINEAL PROSTATECTOMY ON SELECTED CASES OF ADVANCED PROSTATIC CARCINOMA

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It is not surprising that the marked regression of the carcinomatous prostate that frequently resulted from hormone therapy would very quickly suggest a broadened field of usefulness for the radical perineal prostatectomy in selected cases of advanced carcinoma of the prostate. As far as we were able to determine from the literature, Vallet in 1944 was the first to report the use of this combined therapy in one of these cases, but unfortunately the patient died too soon after the operation to permit any conclusion as to its efficiency. In 1944, Scott and Benjamin reported 2 cases that had been treated by this combined therapy, and Colston recommended its use in selected cases. Earlier in the same year Parlow suggested that the combined therapy might be of definite advantage. In 1947, Colston and Brendler reported the results of this therapy on a series of 7 patients who had been operated upon within a period of 2 years. One of their patients had died of carcinoma in less than a year after operation. In 1948, Parlow and Scott reported having treated 14 cases by this combined therapy and presented 9 of them in detail; all of their patients were alive and apparently well at that time.

Inasmuch as any attempt to evaluate the efficiency of this combined therapy in the treatment of selected cases of advanced carcinoma of the prostate gland must take into consideration the type of case included in such a study, we believe it might be helpful if the factors that influenced us most in the selection of our cases were presented at this time. Of course those patients, in whom, because of recent origin or latency of growth, the carcinoma when first seen was so situated as to permit a reasonable chance for its complete removal by radical surgery should not be included in a study of this kind. All patients with proven metastasis when first seen should not be treated by this combined therapy regardless of the response to hormone therapy. Patients without metastasis in whom the local growth is a little too extensive to permit radical surgery when first seen, who fail to respond to hormone therapy, are not suitable candidates for the combined therapy. Where the local growth has advanced to such an extent as to result in the formation of a well-defined intervesicular plateau when the patient is first seen, it seems reasonable to assume that lymphatic and perineural extension beyond the palpable area has occurred even though the presence of metastasis cannot be proven. In such cases the follow-up radical perineal prostatectomy, while it might increase the patient's life expectancy and freedom from distressing symptoms, should still be considered of questionable value. However when the above have been excluded there still remains a very encourag-

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ing number of patients with carcinoma of the prostate from whom the cases to be treated by the combined therapy can be selected.

These are the patients in the group of advanced carcinoma of the prostate without metastasis in whom the carcinomatous extension beyond the confines of the prostate, while not marked, is too great to permit its complete extirpation by radical surgery when the patient is examined. It is for the patients in this group, providing their response to hormone therapy has been such that a digital examination at the time of maximum regression suggests that complete extirpation of the carcinomatous lesion might be possible, that we believe a follow-up radical perineal prostatectomy offers a chance for a cure or failing in this will at least prolong the patient's life and freedom from distressing symptoms. But even some of these patients have to be excluded because advanced age or their general physical condition seem to contraindicate radical surgery.

It seems to us that the decision as to whether or not the patient is a suitable candidate for radical surgery is less difficult to make on the basis of his age than from the standpoint of his general physical condition. Because of their limited life expectancy and because carcinoma of the prostate is often a very slow process in patients who are 80 or more years of age, we have not used the combined therapy in any instance where the patient was that old when first seen. We have learned that as a result of careful preoperative and postoperative care, proper supporting measures during operation and the availability of very satisfactory antibiotics, the radical perineal prostatectomy, while sometimes requiring a little longer to perform, is seldom more disturbing to the patient than some of the more commonly used surgical procedures upon the prostate. At least 2 of our patients had a history of coronary disease with cardiographic evidence of damage and yet were no more disturbed by the operation than the average case. As a rule the operative risk due to the presence of general physical disability is little, if any greater than that of the other open operations upon the prostate for the correction of prostatic obstruction.

Up to the present time in the urological clinic of the Strong Memorial Hospital, we have treated 22 patients by this combined therapy. Of these we are reporting in detail 13 who have been followed 36 or more months since treatment was instituted. The remaining 9 patients have been treated too recently to justify any attempt to evaluate the efficiency of this therapy upon them. Clinical, serological and radiographic studies were negative for the presence of metastasis in the cases to be reported below. Furthermore all blood studies and renal function tests were within normal limits at the time of operation.

CASE REPORTS

Case 1. W. A., S. M. H., 192655, aged 58 when first seen on June 22, 1942 complained of gradual decrease in the size and force of his urinary stream. His father had died of carcinoma of the bowel.

His general physical condition was good except for a right inguinal hernia and a prostate that was enlarged in all diameters and was very hard but for a small area of second degree induration involving about one third of the left lobe towards the base. The very hard area extended from a point a little beyond the base of the prostate and slightly into the region of the right seminal vesicle, down to the middle of the gland where it swung across to the left border. The apex was involved right down to the membranous urethra (fig. 1, *A*). There was a residual urine of 200 cc.

A study of a prostatic biopsy specimen revealed adenocarcinoma.

On July 13, 1942 an orchiectomy was performed and in August 1944, the cancer had regressed and softened so that there was but slight induration in the regions of the right outer border and base of the gland (fig. 1,B). Radical surgery was advised and rejected. However on November 2, 1945 the patient returned because of a slight recurrence of urinary symptoms and some increase in the size and induration of the base of the right lobe was discovered. He was placed on stilbestrol, 5 mg. a day, and his symptoms improved but his prostate remained about the same (fig. 1,C).

A radical perineal prostatectomy was performed on January 22, 1946; the patient was discharged 23 days later. His control was fairly good at that time but was not perfect until 5 months afterwards.

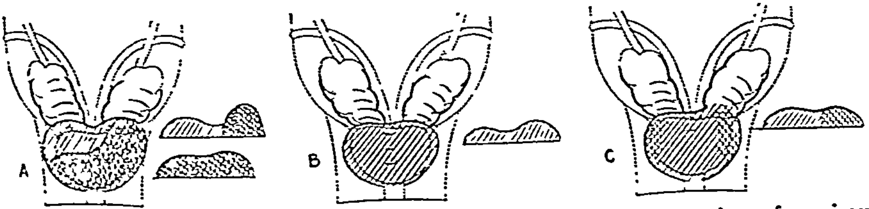


FIG. 1. *A*, prostate before orchiectomy on July 9, 1942. *B*, condition at time of maximum improvement on August 8, 1944, when prostatectomy was rejected. *C*, situation before radical prostatectomy on January 22, 1946 after 5 months of stilbestrol therapy.

Pathological studies of many sections from the surgical specimen failed to show typical carcinoma cells although the connective tissue structural appearance simulated that of adenocarcinoma of the prostate. Perhaps if serial sections of the entire specimen had been made, nests of typical cells would have been found.

The patient has been checked at regular intervals and, as of this date, is apparently well.

Case 2. O. J., S. M. H., 237491, aged 61, when first seen on September 17, 1943 complained of gradually increasing frequency, dysuria and dribbling of 3 years' duration.

He appeared to be in good physical condition but on rectal examination a prostate that was very hard and enlarged in all diameters was found. There was extension of third degree induration beyond the base to the region of both seminal vesicles (fig. 2, *A*). Pathological study of a punch biopsy specimen revealed adenocarcinoma.

Stilbestrol therapy of 5 mg. a day gave considerable relief of urinary symptoms but regression was slow so an orchiectomy was performed on April 5, 1945 and stilbestrol was continued. Four months later regression and softening in the prostatic area had become so marked that radical surgery seemed indicated (fig. 2, *B*).

He was operated on September 9, 1945 and his convalescence was uneventful except that he had almost complete incontinence for a period of 2 weeks following the removal of his catheter. He was discharged 28 days after operation and at that time his control was better but not perfect.

Pathological studies of the specimen showed adenocarcinoma.

All studies for recurrent cancer have been consistently negative and his urinary incontinence is only present on occasions of extreme physical fatigue.

Case 3. C. D., S. M. H., 211137, aged 72 when first seen on November 1, 1943, gave a history of gradual diminution in size and force of his urinary stream, increasing frequency and terminal dribbling of 6 months' duration. There had been no loss of weight.

The findings on physical examination were normal for a man his age except for the prostate which was moderately enlarged in all diameters, its median furrow and notch were shallow, its surface was moderately smooth but very hard, it was fixed in position and extension to the region of the seminal vesicles for a short distance had occurred on each side (fig. 3, *A*). His residual urine was 15 cc and a punch biopsy study revealed adenocarcinoma of the prostate.

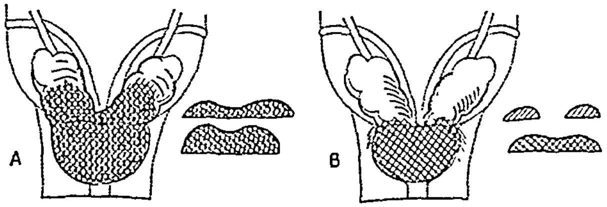


FIG. 2. *A*, prostate before stilbestrol therapy on July 2, 1943. *B*, condition after supplementary orchiectomy on July 17, 1945 and before prostatectomy on September 9, 1945.

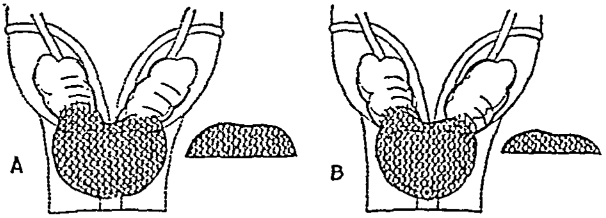


FIG. 3. *A*, prostate before orchiectomy on November 11, 1943. *B*, condition at time of prostatectomy on November 14, 1944.

Following orchiectomy, performed on November 22, 1943, regression which was slow and not marked except in the anteroposterior diameter of the gland, reached its maximum point on November 14, 1944 when a follow-up radical perineal prostatectomy was performed. At that time there still remained some induration extending for a short distance towards the seminal vesicle in each side (fig. 3, *B*).

Pathological studies which were positive for carcinoma suggested the possibility of extension beyond the borders of the surgical specimen in the region of the seminal vesicles.

The patient's convalescence was satisfactory and when he was discharged from the hospital 23 days after operation he was voiding satisfactorily and his control was perfect.

He received no estrogen treatment until a recurrent nodule was discovered on rectal examination 41 months after his prostatectomy. He was immediately placed on stilbestrol therapy which was later supplemented by deep x-ray therapy and local radium treatments and although he is still quite comfortable, it is evident he has not long to live.

Case 4. R. D. G., S. M. H., 218854, aged 56 came to us on May 29, 1944 because a hard nodule discovered in his prostate 6 months before, had been gradually increasing in size. He gave a history of a thrombophlebitis of the right leg many years back and a severe coronary attack with electrocardiographic changes 2 years previously. His father, one sister and one brother had died of cancer.

The prostate was moderately enlarged in all diameters and the median furrow and notch were shallow. In the left lobe towards the base was a very hard, fixed nodule that apparently had either pushed out or broken through the capsular border of the prostate for a distance of about 1 cm. and which was characteristic of cancer (fig. 4, *A*). On stilbestrol 5 mg. daily regression and softening of the nodule were so satisfactory that we were prepared to operate during the latter part of June when a second coronary attack made postponement necessary. His internist, believing that stilbestrol had been a factor in his coronary attack, withdrew the drug with the result that the suspicious nodule had again enlarged but seemed to be contained within the capsule when he entered the hospital on November 19, 1944 for preparation for operation (fig. 4, *B*). Phlebitic enlargement of his right leg and x-ray evidence of arteriosclerotic cardiac disease with left ventricular enlargement were also found. Electrocardiograph studies indicated a very considerable amount of cardiac damage.

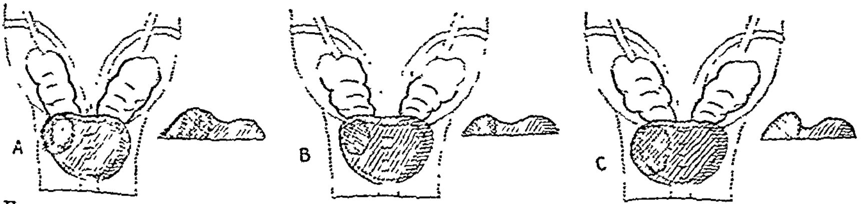


FIG. 4. *A*, prostate before stilbestrol therapy on May 5, 1944. *B*, condition at time of withdrawal of stilbestrol on June 26, 1944. *C*, prostate at time of radical operation on November 3, 1944, showing recurrence of tumor following stilbestrol withdrawal.

On November 21, 1944 a radical perineal prostatectomy was performed and his convalescence was quite satisfactory. He was discharged 15 days after operation and at that time his urinary control was fairly good but not quite perfect.

Pathological studies were especially interesting in that it appeared as though perineural extension of the carcinoma beyond the border of the surgical specimen had occurred in one place.

Four months after operation he was placed on 1 mg. of stilbestrol every other day and 13 months later had a third coronary attack. His control became perfect but unfortunately he died of a primary carcinoma of the stomach 64 months after endocrine therapy had been started and 59 months after his operation. A very careful, complete autopsy failed to reveal any remaining prostatic cancer in the perineal region and no metastases could be demonstrated. All blood phosphatase studies remained normal.

Case 5. H. D., S. M. H., 245467, aged 72, who was admitted to the hospital on December 10, 1944 in complete urinary retention, gave a history of progressive frequency and difficulty with voiding of about a year's duration.

His prostate was markedly enlarged in all diameters, irregular and stony hard. Induration into the periprostatic tissue and over the lower borders of the seminal vesicles was present (fig. 5, *A*).

The patient was placed on catheter drainage and a punch biopsy study of the prostate was made and found positive for carcinoma.

An orchiectomy was performed on December 20, 1944 and when the catheter was removed several days later, he voided without too much difficulty. He was sent home on 1 mg. of stilbestrol a day.

The carcinoma regressed and softened to the extent that there remained only a small hard nodule in the base of the left lobe and extending but a short distance over the left seminal vesicle (fig. 5, *B*).

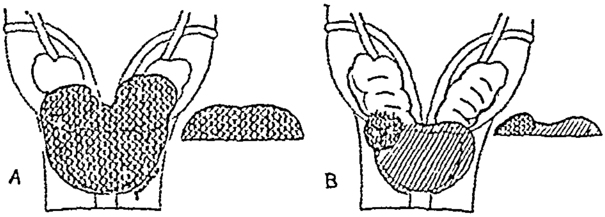


FIG. 5. *A*, extension of prostatic cancer before orchiectomy on December 12, 1944 and start of stilbestrol therapy. *B*, condition at time of radical operation on April 26, 1946.

His convalescence following the radical perineal prostatectomy on March 26, 1946 was uneventful and the patient was discharged with good urinary control 18 days later.

Pathological studies of the surgical specimen revealed carcinoma.

The patient has been followed at regular intervals and there has been no evidence of a return of the carcinoma.

Case 6. C. L., S. M. H., 231376, aged 59, was first seen on April 30, 1945 complaining of hesitancy, frequency and decrease in size and force of stream of 3 months' duration. He gave a history of valvular heart disease following rheumatic fever in childhood and 2 years before we saw him he had suffered a slight cerebral accident but there was no residual paralysis.

On rectal examination the prostate was found to be enlarged in all diameters and the median furrow and notch were shallow. In the right lobe was a large stony hard nodule that extended from the apex to the seminal vesicle and seemed to have pushed out or broken through the lateral border of the capsule. There was moderate induration extending up and over the right seminal vesicle for a short distance. The left lobe was soft and only slightly enlarged (fig. 6, *A*).

A diagnosis of carcinoma of the prostate was made and the patient placed on 5 mg. of stilbestrol twice a day.

On July 19, 1946, two days before his radical prostatectomy, he was free from symptoms, his residual urine was only 80 cc and his prostate had become soft and had regressed to a degree where radical surgery was considered advisable (fig. 6, *B*). A little difficulty was encountered in freeing the right seminal vesicle and its covering fascia from the adjacent tissues because of dense adhesions. He left the hospital 21 days after operation and his control was fair but improved rapidly and was perfect within a few weeks.

A report by his urologist on April 15, 1950 resulted in negative findings and the patient is apparently well.

Case 7. G. A. W., S. M. H., 281682, aged 65, was first seen on June 18, 1948. Three years previous he consulted a urologist in another clinic who made a diagnosis of prostatic cancer and placed him on stilbestrol therapy. The carcinoma regressed and the patient was referred to us for radical surgery.

At that time the left lobe of the prostate was still of third degree induration and extension beyond the lateral border was felt to be present in one area (fig. 7, *A*). Orchiectomy was advised and within a few days the operation was performed.

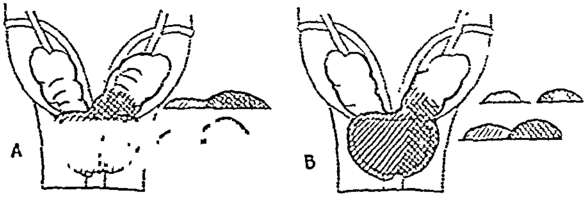


FIG. 6. *A*, prostate before stilbestrol therapy on April 30, 1945. *B*, condition before prostatectomy on July 16, 1946.

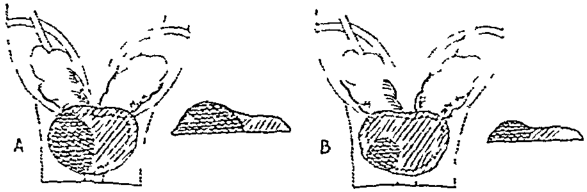


FIG. 7. *A*, prostate when first seen after 36 months of stilbestrol therapy which was started elsewhere. *B*, condition before radical operation on November 2, 1948, 5 months after orchiectomy was combined with stilbestrol therapy.

The regression and softening of the carcinomatous area were so satisfactory that at the time of his prostatectomy on November 4, 1948 there remained only a small nodule located well within the border of the prostate. (fig. 7, *B*).

On November 4, 1948 a radical perineal prostatectomy was carried out with no difficulty. When discharged from the hospital 30 days after operation, the patient had no complaints referable to the act of urination.

Pathological examination showed carcinoma of the prostate.

The patient has resumed his normal life. He has been seen at regular intervals and there has been no clinical, x-ray or serological evidence of a return of the cancer.

Case 8. C. D., S. M. H., 210355, aged 61 when first seen in October 1943, in the course of a routine examination was found to have enlargement of the prostate gland with an area of second degree induration in the outer and upper third of the right lobe, which although it seemed to be benign, was sufficiently suspicious so that the patient was advised to return for another examination in a month. During the next 6 months no change in the prostate was noted. He was next seen in August 1945, at which time the area of induration had become very hard and had definitely increased in size and seemed to have extended beyond the base and outer right border of the prostate (fig. 8, *A*). He was again lost until November 5, 1945 when punch biopsy studies of the involved area were made and found positive for cancer.

He was placed on 10 mg. of stilbestrol a day and the nodule softened considerably and regressed so much that on March 26, the day of his radical operation, it seemed to be confined within the prostatic capsule (fig. 8, *B*).

His heart showed definite evidence of coronary lesion trouble. There was a harsh systolic murmur and considerable enlargement with left ventricular preponderance. The electrocardiogram revealed a bundle branch block.

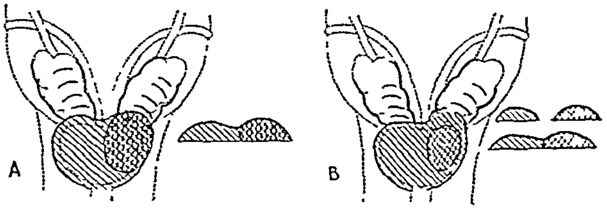


FIG. 8. *A*, prostate when patient was first seen on November 12, 1945 and placed on stilbestrol. *B*, condition before prostatectomy on April 11, 1946.

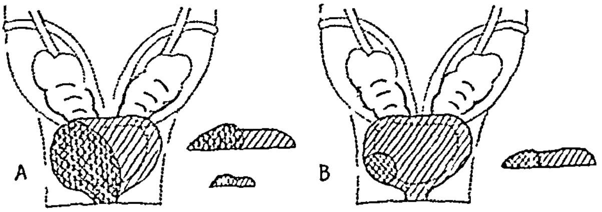


FIG. 9. *A*, prostate when first examined on December 19, 1945. *B*, prostate at time of prostatectomy on October 10, 1946.

He stood his operation very well and when discharged, 19 days later, was voiding with a good stream and good control. A recent examination revealed no evidence of recurrence and he has had no complaints referable to his urinary tract.

Case 9. W. F. D., S. M. H., 241866, aged 65, complained of a decrease in force and caliber of his urinary stream and increasing frequency of several weeks' duration when first seen on December 19, 1945.

He appeared to be in good general physical condition. His prostate was definitely enlarged in its lateral and anteroposterior directions and the median furrow and notch were shallow. The left lobe was practically filled by a stony hard nodule which seemed to extend beyond its borders laterally and at the apex (fig. 9, *A*). This area was so characteristic of carcinoma that a punch biopsy study was not made.

The patient was placed on 10 mg. of stilbestrol daily and regression was so satisfactory that by October 17, 1946, the day of his radical prostatectomy, there remained only a small nodule of second degree induration in outer and lower half of the left lobe (fig. 9, *B*).

He developed phlebitis of the left leg 14 days after operation which resulted in some residual edema at the time of his discharge 44 days after operation. His control was not complete when he left the hospital but became perfect shortly afterwards. One area in his gross surgical specimen at the time of operation appeared to be characteristic of carcinoma. The first sections that were studied showed no carcinoma and unfortunately repeat sections could not be made because the surgical specimen had been destroyed.

After operation the patient discontinued his stilbestrol therapy and in September 1949, a small recurrent nodule about the size of a dime in its greatest diameter was found a little to the left of midline and about 3 cm. inside the anal sphincter. This area was radiated by means of a radium needle containing the element and as a result of this therapy or an orchiectomy which was performed on October 4, 1949, has completely disappeared.

In the absence of histopathological proof of carcinoma we have included this case for the following reasons: 1) In similar cases we have found it necessary to cut numerous repeat sections before finding a microscopic area of carcinoma, 2) the gross specimen suggested the presence of carcinoma, 3) the response to estrogen therapy was similar to that which we have seen in proven carcinoma of the prostate, and 4) the recurrence was characteristic of carcinoma.

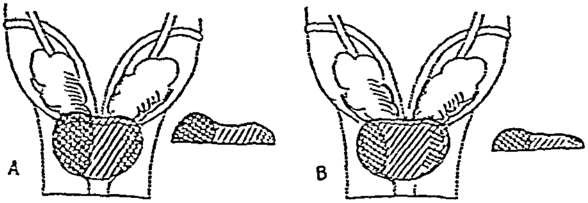


FIG. 10. *A*, prostate before orchiectomy on August 24, 1946. *B*, condition at time of prostatectomy, 9 months after stilbestrol therapy had been added.

Case 10. R. DeF., S. M. H. 213732, aged 62, was first seen in 1945. He complained of frequent and difficult urination. A transurethral prostatic resection was performed on August 3, 1945 and urinary extravasation occurred. Following a suprapubic cystostomy and drainage of the space of Retzius on August 4, 1945, his recovery was rapid and quite satisfactory.

Pathological examination revealed no carcinoma.

On August 10, 1946 he returned complaining of hematuria and a second transurethral prostatic resection was carried out 7 days later.

Pathological examination showed carcinoma of the prostate.

He was given stilbestrol 5 mg. three times daily. On January 7, 1947 rectal examination revealed the left lobe of the prostate to be of third degree induration that extended over the seminal vesicle for a short distance (fig. 10, *A*).

Because response to estrogen therapy was slow, an orchiectomy was performed on July 22, 1947. Following this the carcinomatous nodule softened and apparently regressed to within the confines of the prostate (fig. 10, *B*).

On April 4, 1948 a radical perineal prostatectomy was carried out with little difficulty. The patient had an uneventful convalescence and was discharged from the hospital 21 days later.

Pathological studies revealed carcinoma of the prostate.

The patient has been followed at regular intervals. He has no complaints referable to the act of urination and there has been no clinical or serological evidence of a return of the cancer.

Case 11. A. B., S. M. H., 254201, aged 62, was admitted to the hospital on October 6, 1946, complaining of urine leakage through a suprapubic incision following the removal of bladder calculi 3 months previously in another city. He gave a history of frequent and difficult urination beginning in 1941, complicated by hematuria 4 years later. There was a past history of active pulmonary tuberculosis.

The patient seemed to be in good physical condition. Examination showed the prostate to be enlarged in all diameters. Occupying most of the right lobe and extending up for a short distance in the region of the right seminal vesicle was a very hard, irregular mass which was fixed and clinically characteristic of carcinoma (fig. 11, *A*). Prostatic biopsy studies were negative for carcinoma and there was no x-ray or serological evidence of metastasis. It was our opinion that he had a prostatic cancer which was too extensive to permit complete extirpation at that time.

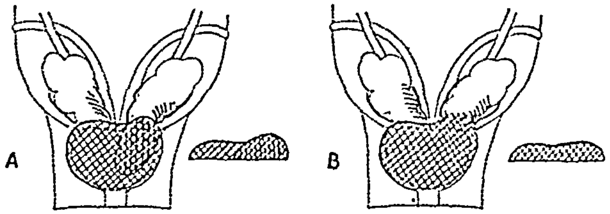


FIG. 11. *A*, prostate before combined orchiectomy and stilbestrol therapy was started in October 1946. *B*, situation at time of prostatectomy on May 8, 1948.

On October 8, 1946 a bilateral orchiectomy was performed and the patient was placed on stilbestrol 5 mg. per day. The prostate regressed in size and became softer and the fistula quickly closed. By April 4, 1948 the carcinoma had apparently regressed to within the confines of the prostate except for a slight extension over the right seminal vesicle (fig. 11, *B*).

On May 8, 1948 a radical perineal prostatectomy was carried out with no difficulty. His convalescence was uneventful. The catheter was removed 14 days after operation and when he was discharged from the hospital 6 days later, he had no complaints referable to the act of urination.

Pathological examination revealed carcinoma of the prostate with stilbestrol effect.

The patient has been followed at regular intervals since leaving the hospital. He has resumed his normal life and is bothered only by occasional hot flashes. There has been no physical, x-ray, or serological evidence of a return of the disease.

Case 12. D. M. D., S. M. H., 280226, aged 63, was first seen on May 28, 1948. He complained of difficulty in starting the urinary stream and dribbling during the previous 18 months.

The patient, a fleshy, white male, appeared to be in good physical condition. Digital examination showed the prostate to be moderately enlarged in all diameters. The left lobe was smooth and elastic. On the outer portion of the right lobe there was an area of third degree induration that extended beyond the confines of the prostate, reaching from the apex almost to the base (fig. 12, *A*). A biopsy study showed carcinoma of the prostate.

He was given stilbestrol 25 mg. per day. On this therapy the prostate regressed definitely in size. The patient, however, was unable to tolerate the drug and on August 12, 1948 a bilateral orchiectomy was performed. Following this operation the prostate continued to regress in size and became softer. Eight months later it was felt that radical surgery was feasible (fig. 12, *B*).

On April 12, 1949 a radical perineal prostatectomy was performed. The catheter was removed 14 days following operation. Four days later the patient was discharged from the hospital. At this time he had no complaints referable to the act of urination.

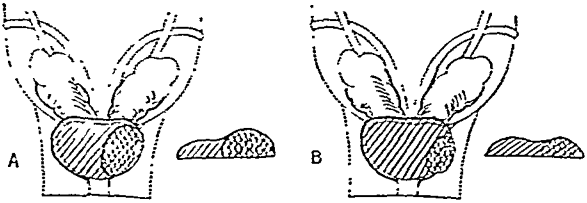


FIG. 12. *A*, prostate after intermittent stilbestrol therapy of 18 months' duration started elsewhere. *B*, condition at time of prostatectomy, 10 months after orchiectomy was combined with stilbestrol therapy.

Two months later the patient developed frequent urination and some incontinence. A short time later he passed a stone following which the incontinence and urinary symptoms disappeared. As of this date there has been no physical, serological or radiographic evidence of return of the cancer.

Case 13. F. E. W., S. M. H., 263048, aged 64, was first seen on April 25, 1947. He complained of frequent urination associated with a gradual diminution in the force and caliber of the urinary stream during the previous 9 months. There was no history of loss in weight, hematuria or back pain.

Physical examination revealed a white male apparently in good physical condition. On rectal examination the prostate was definitely enlarged in all diameters. It was smooth, fixed and of second degree consistency on the right. On the left the consistency was stony hard and there was extension to the seminal vesicles (fig. 13, *A*).

Biopsy studies of the prostate revealed cancer.

He was given stilbestrol 5 mg. per day and his urinary symptoms disappeared. The carcinomatous area softened and regressed so satisfactorily as to permit radical surgery (fig. 13, *B*).

On July 5, 1947 the prostatectomy was performed. This procedure was complicated by a tear in the rectum which fortunately was discovered and closed. The wound healed uneventfully and the catheter was removed 16 days following the operation. When discharged from the hospital 2 days later he was voiding a stream of good force and caliber and had perfect control.

Pathological studies revealed carcinoma of the prostate with extension to the tissue about the seminal vesicles.

The patient was followed at regular intervals and on September 5, 1947 he complained that he was having some difficulty in voiding. A cystoscopic examination revealed a stricture at the vesical neck that was resected following which the urinary symptoms disappeared.

Pathological studies revealed granulation tissue with no evidence of malignancy.

The patient has gone back to work, feels well and has no complaints referable to the act of urination. Frequent studies have shown no clinical or serological evidence of a recurrence of the cancer, either local or metastatic.

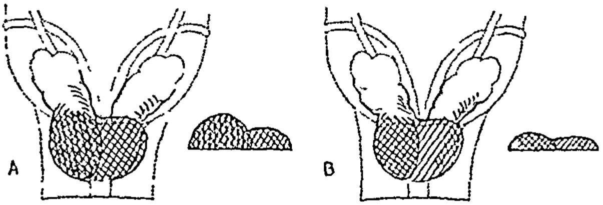


Fig. 13. A, prostate at time stilbestrol therapy was started on April 25, 1947. *B*, condition at time of radical prostatectomy on July 5, 1947.

RESULTS AND DISCUSSION

The results of endocrine therapy plus radical perineal surgery in our first 13 cases, presented above, have been most encouraging. All of these patients have been under treatment 36 months or more. The average time that has elapsed since the institution of endocrine therapy is 62 and the longest 95 months. The average time that has passed since the radical perineal prostatectomy was performed is 41 months; the longest interval 67 months and the shortest 13. The only death in this series (case 4) was due to a primary carcinoma of the stomach that occurred 64 months after endocrine therapy was started and 59 months after prostatic surgery. A very complete autopsy was performed and a special search was made for recurrent or residual carcinoma in his perineal region because pathological studies of the surgical specimen suggested that extension beyond its border had occurred in one place. No tumor was found and metastasis from the original growth was not demonstrated. Neither of the two patients with local recurrence continued his estrogen therapy after prostatic surgery. In our first patient in whom this was discovered, histopathological studies of the surgical specimen suggested that carcinoma has been left beyond its borders in the region of each seminal vesicle. When the recurrence was found, 41 months after prostatectomy, he was placed on stilbestrol which was later supplemented by deep x-ray and local radium therapy. While at the present time, 26 months later, the patient is comfortable, it is evident he has not long to live. The second patient (case 9) was the one where the surgical specimen was lost shortly after the sections for pathological study, which were negative for cancer, were cut. The remaining patients in this group are apparently quite well.

Due to a study by the members of the Urosurgical Society of the results of endocrine therapy on a series of 540 cases of carcinoma of the prostate that were without metastasis when first seen, a very satisfactory yardstick has been obtained for measuring the efficiency of other types of therapy upon patients in this stage of the disease (table 1). It is interesting to note that better results were obtained where orchiectomy and stilbestrol therapy were combined than when either one was used alone. When these results are compared with a control series by Nesbit and Plumb, consisting of 388 similar cases which were treated by the methods in common use before the introduction of endocrine therapy, we find that only 34 per cent of the former as against 70 per cent of the latter were dead at the end of 36 months. While we believe it would be unwise to attach too much significance to the results of a comparative study between a control series consisting of 540 cases, such as that of the Urosurgical Society, and our small series of 13 cases, we would like to point out that all of our patients were living at the end of 36 months, whereas 34 per cent of the patients treated by stilbestrol and orchiectomy combined were dead and 66 per cent of the deaths were due to cancer of the prostate.

TABLE 1. *Per cent survival at 6 month intervals of 540 cases of carcinoma of the prostate without metastasis treated by endocrine therapy. (From study by Urosurgical Society.)*

	MONTHS						NUMBER ELIGIBLE	PER CENT DEAD NOT DUE TO CA
	6	12	18	24	30	36		
Stilbestrol	90.7	82.2	75.6	69.1	56.2	49.7	142	34%
Orchiectomy	91.6	84.9	74.0	65.9	62.2	53.4	239	26%
Orchiectomy and stilbestrol	95.6	89.3	82.3	76.0	70.0	66.0	159	37%
Total cases							540	

It appears that when orchiectomy and stilbestrol are combined in treatment of cancer of prostate, result is more satisfactory than when either is used separately.

We believe that our results are sufficiently encouraging to warrant further trial of this therapy, not only by us, but by others. Even if the results in our remaining cases are not as good, and we doubt that they will be, we believe that this treatment in most instances, where judiciously used, will prolong the life of the patient and increase his period of freedom from the distressing urinary symptoms that almost inevitably accompany the late stages of this disease. As pointed out previously, the operation entails little or no more risk than other open operations for relief of prostatic obstruction. Furthermore, the introduction of the "traction suture" method of closure by Vest has done much to prevent incontinence that occasionally resulted from this type of surgery.

In some cases of carcinoma of the prostate in which the response to endocrine therapy has been very satisfactory, it is sometimes very difficult to demonstrate

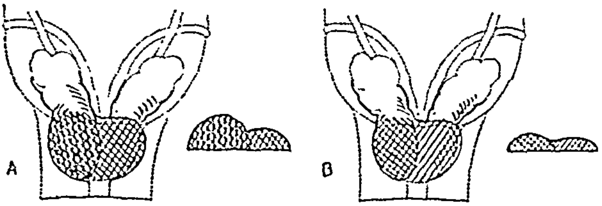
On July 5, 1947 the prostatectomy was performed. This procedure was complicated by a tear in the rectum which fortunately was discovered and closed. The wound healed uneventfully and the catheter was removed 16 days following the operation. When discharged from the hospital 2 days later he was voiding a stream of good force and caliber and had perfect control.

Pathological studies revealed carcinoma of the prostate with extension to the tissue about the seminal vesicles.

The patient was followed at regular intervals and on September 5, 1947 he complained that he was having some difficulty in voiding. A cystoscopic examination revealed a stricture at the vesical neck that was resected following which the urinary symptoms disappeared.

Pathological studies revealed granulation tissue with no evidence of malignancy.

The patient has gone back to work, feels well and has no complaints referable to the act of urination. Frequent studies have shown no clinical or serological evidence of a recurrence of the cancer, either local or metastatic.



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In some cases of carcinoma of the prostate in which the response to endocrine therapy has been very satisfactory, it is sometimes very difficult to demonstrate the presence of residual carcinoma by means of microscopical studies of sections from the surgical specimen. We have had that experience in two of our recent cases. In both of these a clinical impression upon rectal examination by at least two of the senior members of our staff, repeated positive studies of the prostatic secretion prepared by the Papanicolaou method and interpreted by a cytologist especially skilled in this particular field, and regression and softening of the suspected area following endocrine therapy, all pointed so strongly towards carcinoma that a follow-up perineal prostatectomy was performed. Pathological studies of many sections from both specimens repeatedly showed connective tissue formations very similar to those found in cancer of the prostate but the epithelial cells were either absent or so changed by the endocrine therapy that a positive diagnosis of cancer could not be made. It is our belief that had serial section of the entire specimens been made, nests of carcinoma cells would have been found. We have been greatly influenced in reaching this conclusion by an experience in one case and observations made from repeated cytologic studies in others. Pathological studies of a biopsy specimen obtained from the first patient in our series on his initial visit were typical of carcinoma of the prostate. Following orchiectomy and estrogen therapy, a radical prostatectomy was performed 42 months after his first visit. Pathological studies of many sections from his surgical specimen revealed the same connective tissue structural appearance mentioned above but again typical carcinoma cells were not found. Cytologic studies in the two recent cases mentioned above showed progressive effect of endocrine therapy on the malignant cells, which were plentiful when the patients were first examined. In one case, after 6 months of therapy, the malignant cells completely disappeared and remained absent until the radical perineal prostatectomy was performed 2 months later. While the malignant cells in the prostatic secretion of the second patient did not completely disappear, they did decrease markedly in number and showed marked estrogen effect before operation. It would seem that where a decision has been made to try the combined therapy described above and where the operator is unwilling to proceed with radical surgery without positive histopathological support, such studies should be made before endocrine therapy has been instituted.

In our opinion, all patients who have had a radical prostatectomy for cancer of the prostate gland should continue a routine course of some type of estrogenic therapy for a very long time after operation, regardless as to whether they were treated in the manner presented above or belonged to the more fortunate group, in which because of the size and location of the carcinomatous nodule, a preliminary course of endocrine therapy did not seem necessary. It is not always easy to convince some of these patients, who are feeling well and know that the organ which was the source of their trouble has been completely removed, that they must continue estrogen therapy even though at times it may cause some discomfort. However, the reasons for the postoperative continuance of estrogen therapy are so obvious and valid that even the most stubborn patient can be convinced of its necessity without creating a cancer phobia, if patience and discretion are exercised in their presentation.

CONCLUSIONS

The first 13 in a series of 22 selected cases of advanced carcinoma of the prostate that were treated by endocrine therapy combined with a follow-up radical perineal prostatectomy have been presented in detail.

While this report has not been submitted as an evaluation of the ultimate mortality in such cases, we believe the results to date warrant a further trial of this therapy, not only by us, but by others.

REFERENCES

Colston, J. A. C. and Brendler, H.: J. A. M. A., 134: 848, 1947.
Parlow, A. L. and Scott, W. W.: New York State J. Med., 49: 629, 1949.
Scott, W. W. and Benjamin, J. A.: Bull. New York Acad. Med., 21: 307, 1945.
Vallett, B. S.: Delaware State M. J., 16: 19, 1944.
Vest, S. A.: Surg., Gynec. & Obst., 70: 935, 1940.

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A CYTOLOGIC STUDY OF BENIGN AND MALIGNANT LESIONS OF THE HUMAN PROSTATE, URINARY BLADDER AND KIDNEY

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The early diagnosis of malignant lesions of the prostate, urinary bladder and kidney continues to be difficult. When carcinoma of these organs can be removed before extension and metastasis to adjacent and distant tissue have been established, cure is possible. The vast majority of all malignancies are not diagnosed early enough so that radical excision may be successfully accomplished. Usually the diagnosis is made after the disease has extended beyond the tissue of origin.

The only accurate method for diagnosis of carcinoma of the prostate is biopsy. There are three different methods of approach for removal of tissue from the prostate for diagnosis; namely, transurethral resection, perineal exposure of the gland, and lastly, needle aspiration through a perineal approach. Any of these methods is satisfactory if one is certain that the tissue studied is representative of the lesion. Unfortunately, deeply-seated, small carcinomatous areas in the prostate are difficult to locate for satisfactory microscopic study. The diagnosis of carcinoma of the bladder is less difficult in that it may be diagnosed by cystoscopic examination; and the tissue for microscopic study is more accessible. Malignancy of the kidney is usually diagnosed by means of x-ray and pyelographic studies. Occasionally free tumor cells in clear or bloody urine may be obtained and a diagnosis made.

During the past half century the attention of biologists has been drawn to many of the finer details of the cell. Some of these studies indicate that cytologic differences exist in certain instances between neoplastic cells and their cells of origin.[1, 2] These studies have received relatively little attention from the routine pathologists. It has, therefore, seemed to us to be worthwhile to study the Golgi material and mitochondria in benign and malignant prostatic tissue and in carcinomas of the bladder and kidney to try to determine whether there is any difference which may be helpful in establishing a better understanding of these tumors, and more especially, an earlier diagnosis of carcinoma of the prostate.

Read at annual meeting, American Urological Association, Washington, D. C., May 30, 1950.

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[1] Lewis, W. H.: Some cultural and cytological characteristics of normal and malignant cells in vitro. Arch. f. exper. Zellforsch., 23: 8-26, 1939.

[2] Dalton, A. J. and Edwards, J. E.: Mitochondria and Golgi apparatus of induced and spontaneous hepatomas in the mouse. J. Nat. Cancer Inst., 2: 565-575, 1912.

In defining Golgi material we refer to a material within cells which is blackened by osmic acid or by silver salts, is distinct from particulate matter which may be similarly blackened, is interpreted by different writers as fluid, semifluid, and is sharply separated from the surrounding cytoplasm so that its surfaces constitute interfaces on which metals and a few dyes may be absorbed. It has been variously described as a series of canals or vacuoles or as threads of lipoid material. It was originally described as a network but some authors interpret that picture as the result of the fusion of original separate granules. Many present day cytologists interpret this as an artefact of cytoplasmic fixation.[3–5] It sometimes forms a perinuclear cap but it is to be distinguished both from metal precipitated on the nuclear membrane and from lipoid droplets absorbed on the nuclear surface. In epithelial cells, the usual position of the Golgi material is in the cytoplasm distal to the nucleus; that is, between the nucleus and the free surface of the cell.

The function of the Golgi material is still under discussion. Since the identification of the Golgi material and the accumulation of evidence of its presence in most animal cells, many studies have been concerned with its significance. At present the more generally accepted hypothesis is that the Golgi material is in some way concerned with both secretory and excretory functions of the cell.[6, 7]

Next to the nucleus and chromosomes, mitochondria are the most conspicuous and abundant constituent of cells. They have a typical morphology, filamentous or rod-shaped, occasionally granular, with a remarkably constant and uniform width in most cell types. They appear to be self duplicating elements which grow by elongation, dividing across their length. They are universally found in active cells.[6, 8]

Mitochondria are considered to be one of the essential living elements of the cytoplasm. Chemically they contain phospholipids.[9] They apparently are the site in the cell where the energy of molecular oxygen is ultimately transferred and utilized. Important enzymatic activities occur either in or on the surface of mitochondria such as those involving some of the most important respiratory enzyme systems.[10, 11]

Some investigators believe that secretory and pigment granules are derived

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[3] Baker, J. R.: The structure and chemical composition of the Golgi element. Quart. J. Micros. Sci., **85**: 1–71, 1944.

[4] Worley, L. G.: Golgi apparatus: Interpretation of its structure and significance. Ann. New York Acad. Aci., **47**: 1–55, 1946.

[5] Palade, G. E.: On the nature of the Golgi apparatus. Anat. Rec., **103**: 77, 1949.

[6] Cytology and Cell Physiology, G. Bourne, editor. Oxford University Press, 1942. chapters 4 and 8.

[7] Hibbard, H.: The current status of our knowledge of the Golgi apparatus in the animal cell. Quart. Rev. Biol., **20**: 1–19, 1945.

[8] Claude, A.: Studies on cells: Morphology, chemical constitution, and distribution of biochemical functions. Harvey Lectures. series 43, pp. 121–164, 1948.

[9] Bensley, R. R.: On fat distribution in mitochondria of guinea pig liver. Anat. Rec. **69**: 341–353, 1937.

[10] Hogeboom, G. H., Schneider, W. C. and Palade, G. E.: Cytochemical studies of mammalian tissues. I. Isolation of intact mitochondria from rat liver; some biochemical properties of mitochondria and submicroscopic particulate material. J. Biol. Chem., **172**: 619–635, 1948.

[11] Schneider, W. C.: Intracellular distribution of enzymes. III. The oxidation of octanoic acid by rat liver fractions. J. Biol. Chem., **176**: 259–266, 1948.

directly from mitochondria. Such granules are supposed to contain the accumulated products of the metabolic activity of mitochondria.[12, 13]

Mitochondria are considered to give certain staining reactions, particularly a specific one with Janus Green B in low concentrations of the dye.[14]

MATERIALS AND METHODS

The types of material studied are presented in table 1.

Whenever possible normal or uninvolved tissue was obtained for comparative study. Since both the mitochondria and Golgi substance are subject to rapid postmortem change and disintegration, it was necessary that the tissue specimens be placed in the appropriate fixing solution within 15 minutes from the time of interruption of the circulation. Our procedure has been to have the technician assigned to this project attend the operation personally, gowned and masked like the "floating" part of the operating team. The methods used to obtain the specimens were surgical removal of the prostate, kidney and bladder, partial removal of prostatic tissue with the cold punch, and transurethral resection (Bovie).

TABLE 1. *Tissues studied*

Prostate:	
Benign	150
Malignant	32
Total	182
Urinary bladder:	
Controls	55
Malignant	31
Total	86
Kidney:	
Nonmalignant lesions	14
Malignant tumors	7
Total	21

* In 5 of the 32 malignant prostate cases, stilbestrol was given but in each of these cases tissue was obtained both before and after the period of treatment.

The Golgi material was visualized by an osmic acid method (Nassonov modification of Kolatchew's method).[2]

The mitochondria were fixed and stained by a modified Regaud method.[2]

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[12] Woods, M. W., DuBuy, G. H., Burk, D. and Hessebach, M. L.: Cytological studies on the nature of the cytoplasmic particulates in the Cloudman 591 mouse melanoma, the derived Algire S91A partially amelanotic melanoma, and the Harding-Passey mouse melanoma. J. Nat. Cancer Inst., 9: 311–323, 1949.

[13] Dubuy, H. G., Woods, M. W., Burk, D. and Lackey, M. D.: Enzymatic activities of isolated amelanotic and melanotic granules of mouse melanomas and a suggested relationship to mitochondria. J. Nat. Cancer Inst., 9: 325–336, 1949.

[14] Cowdry, E. V.: The general functional significance of mitochondria., Am. J. Anat., 19: 423–446, 1916.

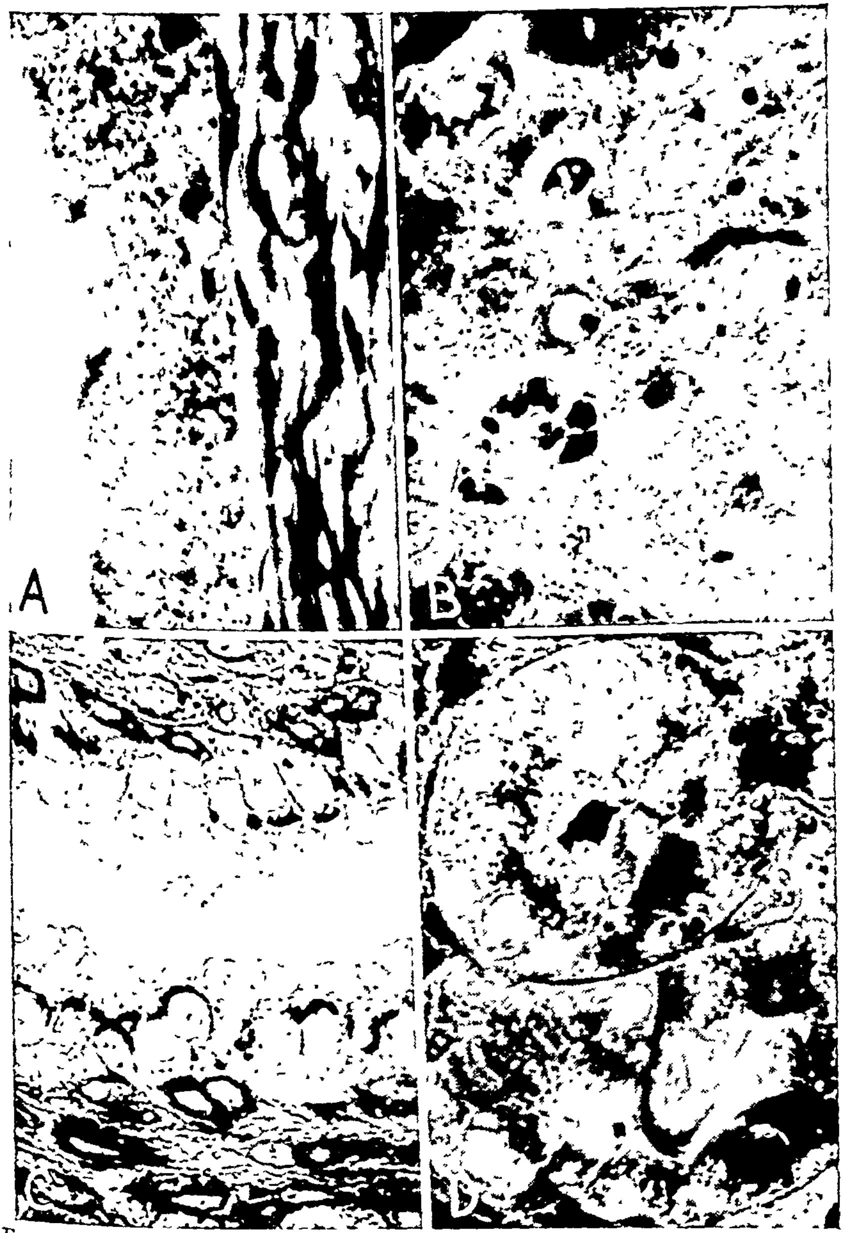

FIG. 1. *A*, mitochondria in cells of benign prostatic hyperplasia. Relatively few in number. × 900. *B*, mitochondria in malignant cells in adenocarcinoma of prostate. Numerous tenuous filaments. × 900. *C*, Golgi material in cells of benign hyperplasia of prostate. Relatively small in amount and located near nucleus. × 900. *D*, Golgi material in malignant cells in adenocarcinoma of prostate. Golgi material is relatively large in amount, extending for a considerable distance toward free surface of the cell. × 900.

RESULTS

Prostate. Observations on lesions of the prostate will be reported in detail elsewhere, so that only a brief summary will be presented here. Mitochondria

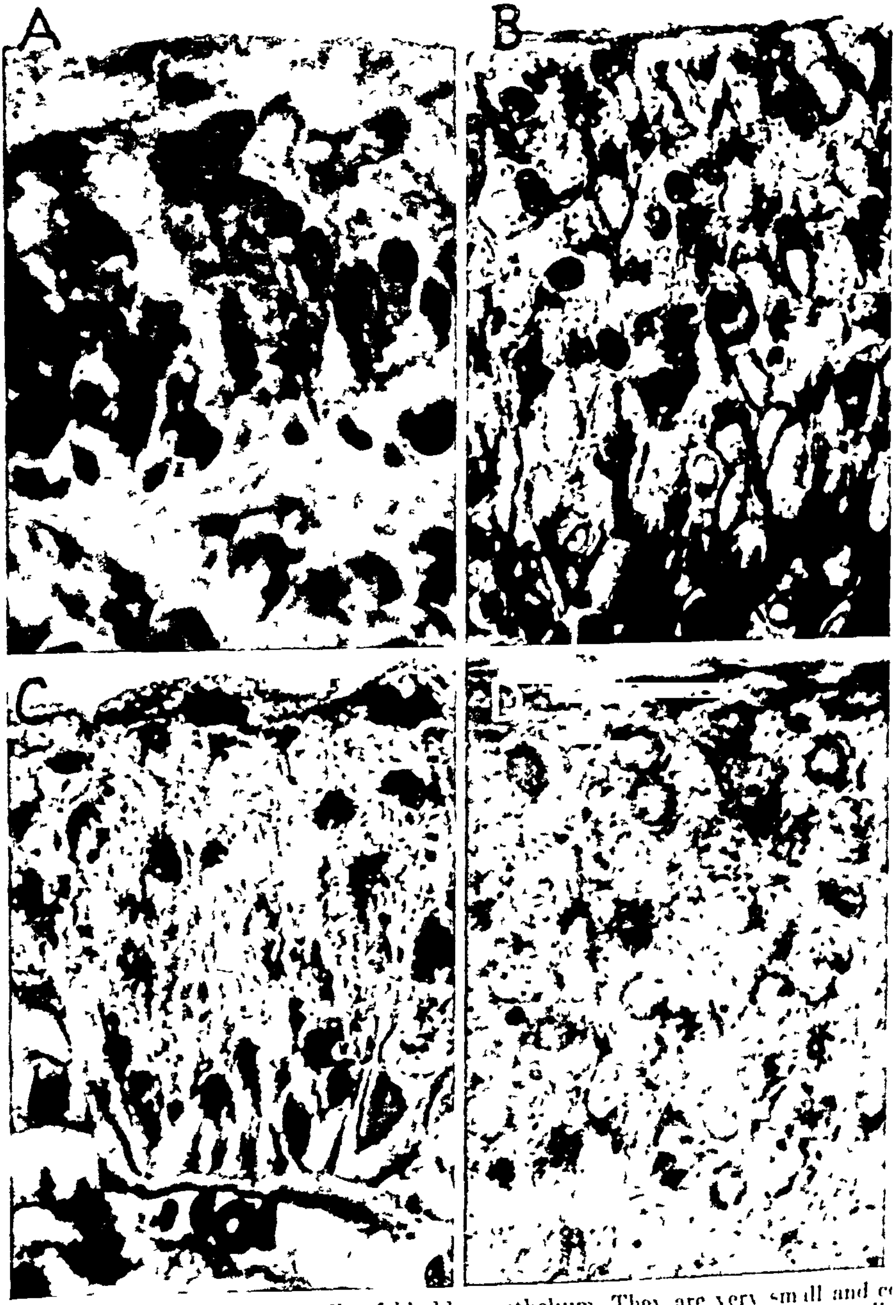

FIG 2 A, mitochondria in cells of bladder epithelium They are very small and concentrated as a perinuclear cap on distal side of nucleus × 900 B, Golgi material in cells of bladder epithelium Small in amount and located in cytoplasm distal to nucleus × 900 C, mitochondria in cells of papillary carcinoma of bladder Concentrated as a large perinuclear cap on distal side of nucleus × 900 D, mitochondria in cells of infiltrating carcinoma of bladder In most cells perinuclear concentration seen in B and C is lacking × 900

in cells of benign hyperplasia are consistently medium sized spheres and filaments with spheres predominating They are relatively few in number and are located in the narrow strands of cytoplasm surrounding the numerous vacuoles characteristic of these cells (fig. 1, *A*). Mitochondria in cells in adenocarcinoma of the prostate were found regularly to be present as numerous fine, tenuous filaments (fig. 1, *B*). The Golgi material showed greater variation than did the mitochondria but in general, it tended to be smaller in amount and located closer to the nucleus in cells in benign hyperplasia (fig. 1, *C*) than in adenocarcinoma of the prostate (fig. 1, *D*).

Urinary bladder. Good control samples of the transitional epithelium of the urinary bladder exhibiting mitochondria and Golgi material were rather difficult to obtain. Contraction of the smooth muscle of the bladder wall before and during fixation resulted in folding of the epithelium and occasionally in separation of the epithelium from the underlying connective tissue. In addition it is characteristic of the method used for the most superficial cells in a block of tissue to contain poorly visualized and preserved Golgi material. There was enough material obtained however, to give us reasonably good examples of the mitochondrial distribution and the pattern of the Golgi material in this control tissue. Mitochondria in cells of the bladder epithelium consisted of very small filaments and spheres concentrated as a distal perinuclear cap (fig. 2, *A*). The Golgi material was found to consist of a rather small amount of osmiophilic material in the form of heavy closely knit strands on the distal side of the nucleus (fig. 2, *B*).

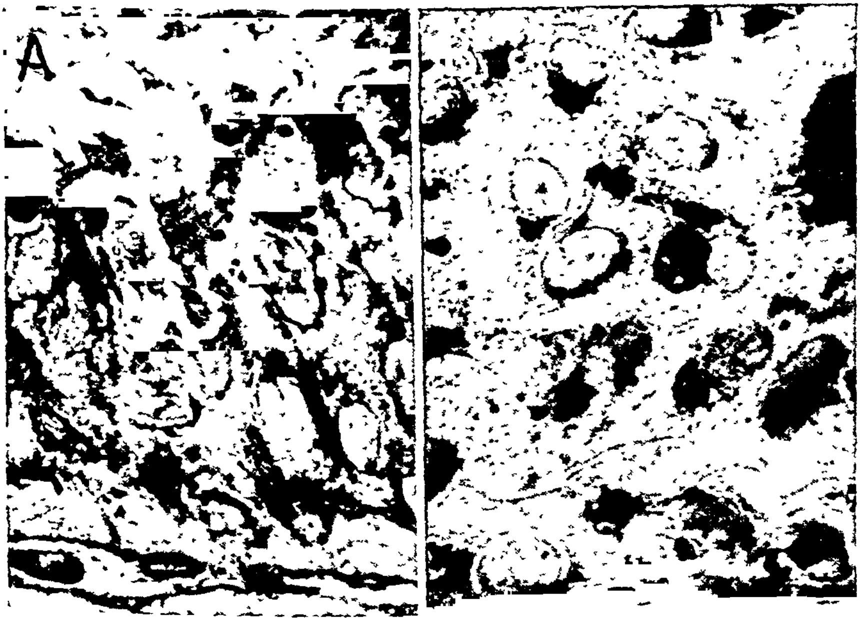

FIG. 3. *A*, Golgi material in cells of papillary carcinoma of bladder. In many cells it is found on proximal rather than distal side of nucleus. × 900. *B*, Golgi material in cells of infiltrating carcinoma of bladder. It appears as a heavy mass of osmiophillic material on that side of cell toward nearest blood vessel. × 900.

Mitochondria in cells of papillary carcinoma of the urinary bladder occupy a larger cytoplasmic area than those in cells of the epithelium of the bladder in control specimens but continue to be oriented as a distal perinuclear cap (fig. 2

C). In the cells of infiltrating carcinoma of the bladder the mitochondria tend to be distributed more evenly throughout the cytoplasm (fig. 2, *D*).

The Golgi material in many cells of papillary carcinoma of the bladder is found to be located near the proximal rather than the distal side of the nucleus suggesting a change in polarity of such cells (fig. 3, *A*). However, a similar shift in the position of the Golgi material is sometimes found in cells of epithelial invaginations in control material. In cells of infiltrating carcinoma of the bladder the Golgi material is found consistently to be located proximally, i. e., between the nucleus and the cell surface nearest connective tissue and blood vessels (fig. 3, *B*).

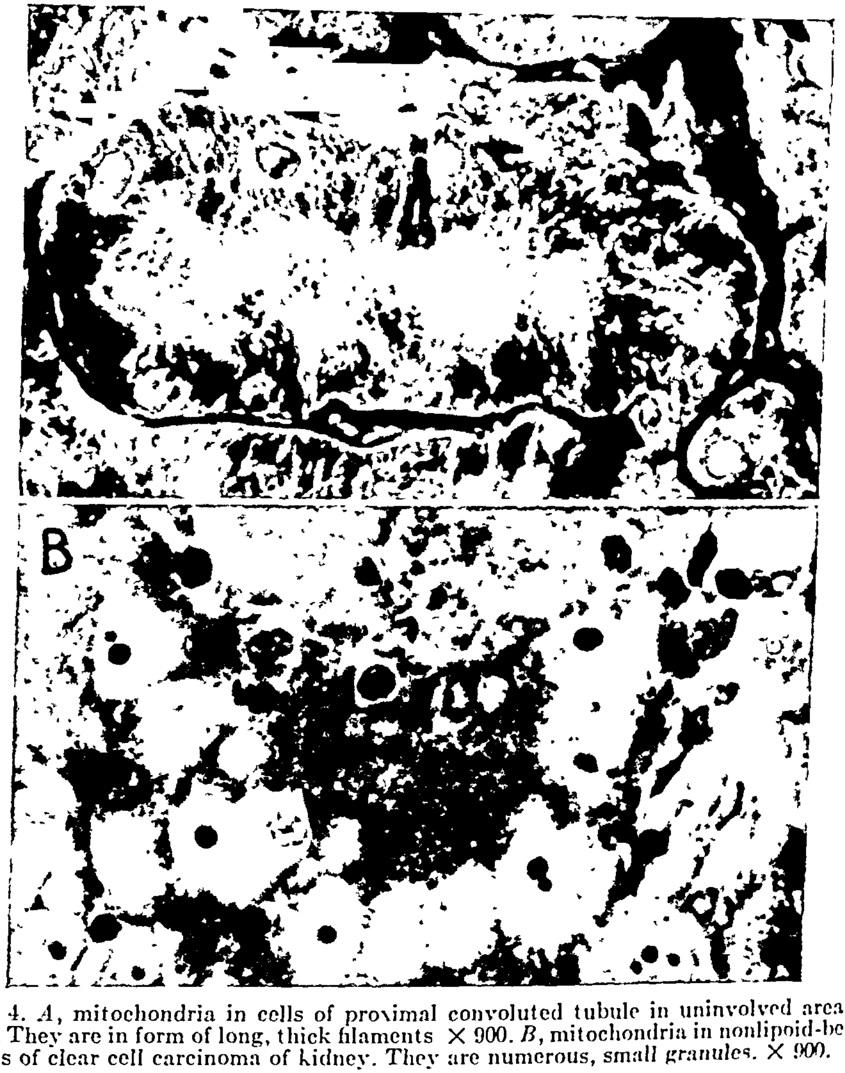

FIG. 4. *A*, mitochondria in cells of proximal convoluted tubule in uninvolved area of kidney. They are in form of long, thick filaments × 900. *B*, mitochondria in nonlipoid-bearing cells of clear cell carcinoma of kidney. They are numerous, small granules. × 900.

Kidney. As was to be expected, we experienced difficulty in obtaining healthy control kidney cells for comparison with malignant cells. Figure 4, *A* shows the mitochondria in proximal convoluted tubule cells from apparently uninvolved

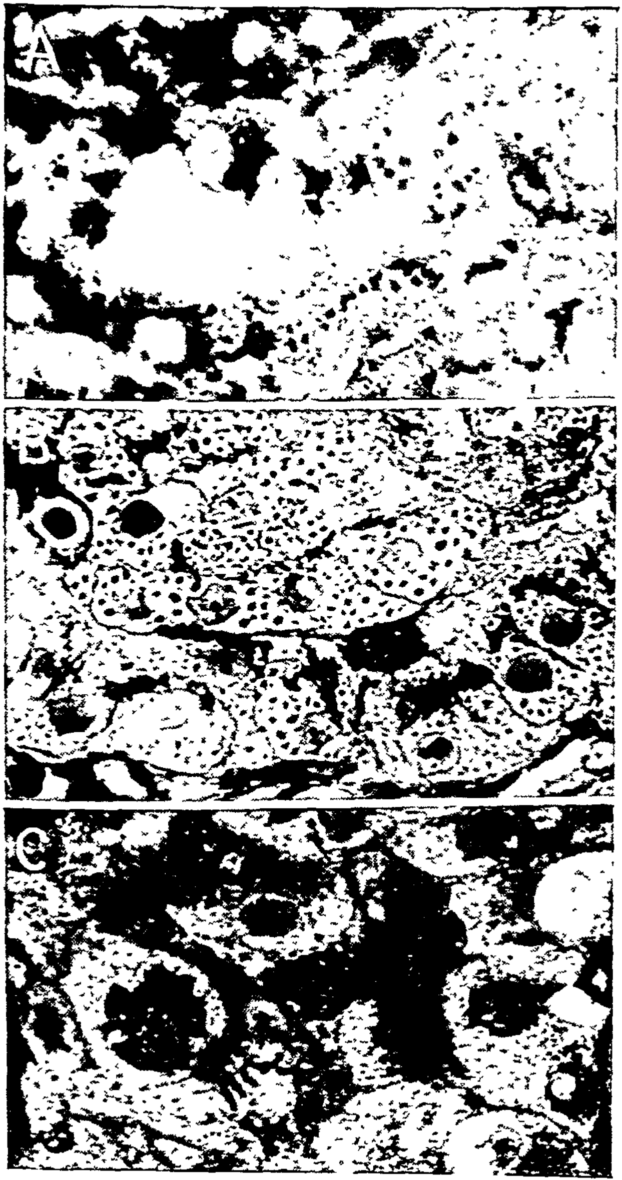

FIG. 5 *A*. Golgi material in cells of proximal convoluted tubule in uninvolved area of kidney. × 900. *B*. Golgi material in lipoid-bearing cells of a clear cell carcinoma of kidney. × 900. *C*. Golgi material in nonlipoid-bearing cells of clear cell carcinoma of kidney. It is greatly increased in amount compared with that seen in *B*. × 900.

tissue in a case of hydronephrosis. Mitochondria of the proximal convoluted tubule cells, however, cannot be considered as typical of all kidney cells. Long, relatively thick, straight filaments are also present in distal convoluted tubule cells but collecting tubule and Henle's loop cells contain moderate numbers of thin tenuous filaments. Epithelial cells of Bowman's capsule contain relatively few small filaments and spheres. In the lipoid laden cells of clear cell carcinoma of the kidney the mitochondria were found to be small spheres, few in number, located in the cytoplasmic areas between the lipoid granules. Areas of clear cell carcinoma are frequently found in which lipoid material is scarce or absent. Cells in such areas contain very numerous small granular mitochondria (fig. 4, *B*). Mitochondria in cells of adenocarcinoma of the kidney are present as rather numerous tenuous filaments.

The Golgi material in cells of uninvolved kidney parenchyma appears as a moderate amount of osmiophilic substance in the form of granules and filaments located between the nucleus and the distal border of the cell (fig. 5, *A*). A not dissimilar picture is seen in other cell types in kidney parenchyma, although the epithelial cells of the glomerulus possess a relatively large amount of Golgi material in proportion to their cytoplasmic area. The Golgi material in cells of adenocarcinoma of the kidney is similar to that found in control kidney parenchyma but in cells of clear cell carcinoma it forms a heavy dense network (fig. 5, *B*). In cells free of microscopically demonstrable lipoid in this type of tumor, the Golgi material is greatly increased in amount (fig. 5, *C*).

DISCUSSION

Fairly consistent differences in mitochondrial number and in the relative amount of Golgi material has been found to exist in cells of benign vs. malignant lesions of the human prostate.[1] The mitochondria of cells in benign hyperplasia were found to be relatively large and few in number while those in cells of adenocarcinoma of the prostate were relatively small but numerous filaments. The Golgi material in cells of benign hyperplasia of the prostate varied somewhat in amount but was regularly found in close proximity to the distal border of the nucleus. Cells of adenocarcinoma contained relatively large amounts of Golgi material frequently located at a considerable distance from the nuclear membrane. These results suggest that increase in number and decrease in size of mitochondria may prove to be an additional criterion of malignancy in this particular instance. The difference in the amount of Golgi material between hyperplastic cells and cells of adenocarcinoma has been a consistent finding. However, the vagaries of the method used to visualize the Golgi material and the fact that only a limited area at the periphery of a section contains good examples probably makes this finding of academic interest only.

It is well known that the histologic structure and organization of carcinomas of the urinary bladder are of little value in prognosis. In other words, tumors with similar histologic structure may give clinical evidence of greatly different growth rates and per cent of recurrence after removal. In the present study, the mitochondrial distribution in cells of papillary carcinomas has been shown to differ from that in infiltrating papillary carcinoma. We have no evidence to indicate that this difference is consistently correlated with differences in growth rate or with the other factors associated with "degree of malignancy." The possibility that such a correlation exists certainly warrants further study of the cytology of this group of tumors. It is also interesting to speculate on the significance of the shift in position of the Golgi material in cells of carcinomas of the urinary bladder. This change in position which sometimes is found in cells of presumably normal bladder epithelium may result from an actual change in orientation of these cells during the process of contraction and thickening of the epithelium at the time of fixation. However, this change is only occasionally found in such epithelial invaginations. The possibility must also be considered that cells exhibiting this reversal in position of the Golgi material are neoplastic. It is possible that they are the visible evidence to be correlated with the facts that papillomas of the urinary bladder are frequently multiple and that recurrence of these tumors may be at a site different from the original locus.

Very little can be said concerning the cytology of the kidney tumors studied so far, the number of tumors studied being too few. The general form and distribution of the mitochondria and the pattern of the Golgi material in cells of adenocarcinoma of the kidney resemble those found in control kidney cells. It can only be stated that the number and size of mitochondria and the amount and pattern of the Golgi material in cells of clear cell carcinoma differ from those seen in any of the parenchymal cells of control kidneys.

SUMMARY

A cytologic study of a series of benign and malignant lesions of the prostate gland, control tissues and malignant lesions of the urinary and nonmalignant and malignant lesions of the kidney has been carried out. Special attention has been given to variations in size and number of mitochondria and to differences in the amount of Golgi material.

Cells of adenocarcinoma of the prostate were found to contain a greater number of mitochondria and an increase in the amount of Golgi material when compared with cells of benign hyperplastic lesions.

The mitochondria of cells of the transitional epithelium of the urinary bladder were found to be concentrated as a perinuclear cap on the distal side of the nucleus. This distribution of mitochondria was found to be retained in papillomas of the urinary bladder but lost in many of the cells of infiltrating papillary carcinoma. The Golgi material, distal to the nucleus in cells of transitional epithelium, was found to be reversed in position in some cells in epithelial invaginations in presumably normal bladder epithelium, in many cells in papilloma of the bladder and in all cells in infiltrating papillary carcinoma.

The number of mitochondria and amount and pattern of the Golgi material were in general similar in adenocarcinoma of the kidney and uninvolved kidney parenchyma. The mitochondria in nonlipoid-bearing cells of clear cell carcinoma were much greater in number and much smaller in size than the mitochondria in any of the cells of uninvolved kidney parenchyma. Similarly, the Golgi material in such cells was greatly increased in amount over that seen in any parenchymal cells of control kidneys.

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DISCUSSION

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Like Dr. Mostofi, I cannot overemphasize the importance of collaborative work of this type. I think that the practicing urologists who see these tumors in all stages of development, tumors of the kidney, tumors of the bladder, tumors of the prostate, would do well to set up similar collaborative studies with men in the basic sciences. Much remains to be done, and it is necessary to use material from human beings, since there is no counterpart for tumors of the kidney and prostate in the lower animal.

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In regard to the possibility of simplifying or shortening the techniques required to visualize mitochondria and Golgi material, the possibility so far as Golgi material is concerned is very slight, but it does seem reasonable that if, with further study, it looks like the approach would be practical, it would be possible to visualize the mitochondria in fresh material, using the phase contrast microscope and using it within a relatively short time after or even during the operation. It would also be possible, by the development of a smear technique and examination of mitochondria immediately, to give probably as quick a review of the material as can be done by the Papanicolaou technique, but that is for the future.

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FINAL REPORT OF A CASE OF TRUE HERMAPHRODITISM WITH REPAIR OF PERINEAL HYPOSPADIAS

W. CALHOUN STIRLING AND ALFRED J. SURACI

In 1946, a preliminary report of a case of true hermaphroditism was made in which male and female elements were found in the same individual. At that time 37 other cases of true hermaphroditism had been reported in which the diagnosis was confirmed by pathologic study. Since that time additional cases have been reported by Davis, Weed, and Segaloff in which the diagnosis was confirmed microscopically.

Hinman states: "Hermaphroditism may be an atavistic recurrence of an earlier ancestral condition and the adult expression of abnormal embryonic potentiality."

During the sixth or seventh week of embryonic life the external genitalia begin to take the form of male or female, and the specific ovarian or testicular hormones come into play and thus lead to the differentiation of the internal and external sexual organs into male or female. In this sex differentiation other glands of internal secretion may begin to play their part. It is well known that hyperplasia of the adrenal cortex is associated with marked change of secondary sex characteristics in the female. It is probable that the hormones from the adrenal cortex have either a direct or indirect masculinizing effect, just as a tumor of the adrenal cortex produces a condition known as virilism, in which a previously normal young woman may suffer atrophy of the breasts, development of hair on the face and abdomen, and rapid growth of a sizable "penis" from the previously small clitoris.

Hermaphroditism is arbitrarily divided into true and false types. The former is germinal or glandular and includes lateral, unilateral or bilateral types, whereas the latter embraces the majority of cases reported. The case herein reported belongs to the lateral type as an ovary was found on one side and a testicle on the other. Doss and Priestley reported one of true hermaphroditism in which an ovotestis was present on each side. They were able to separate these structures and remove the ovarian tissue. McIver reports a similar case but was unable to separate the two gonads. Pseudohermaphroditism is tubular and internal and may be unilateral or bilateral and include either sex. The genital or external type includes either sex as does the psychical or somatic types. True bisexuality embraces approximately 40 cases, whereas the pseudo type includes more than 900 cases, of which 722 were of the masculine variety.

Despite fantastic reports to the contrary, true hermaphroditism does not imply dual sexual capacity as no authentic case has been reported in which the individual was receptive to both male and female. One may find a well developed ovary, but the testicle is generally undescended, and spermatogenesis is absent.

The pseudohermaphrodite, on the other hand, presents bizarre variations of sex, both internal and external. Several cases are cited in which a

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Read at annual meeting, North Central Section, American Urological Association, Des Moines, Iowa, October 29, 1948.

DISCUSSION

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urogram revealed a normal upper urinary tract. Two 10F sounds could be passed simultaneously into the urinary meatus without touching, one into the bladder, the other into the rudimentary vagina which connected to the urethra 3 cm. proximal to the external opening. This cul-de-sac was approximately 8 cm. in length. The labial folds were soft, and gonads could not be palpated either in the labia or in the inguinal canals.

The urine and blood examinations were normal. An estimation of the estrogen, androgen content of the urine indicated androgenic estimation of 59 i.u., estrogenic reading of 20.4 i.u., a ratio of 2.9. The 17-ketosteriods were 10.3 mg. per 24 hour specimen or 7.3 mg. per liter. (Normal male 15 to 20 mg., normal female 5 to 7 mg.). These assays revealed the fact that the individual was bisexual, scarcely more male than female, although the psychological attitude of the patient as well as the secondary sex characteristics were definitely masculine.

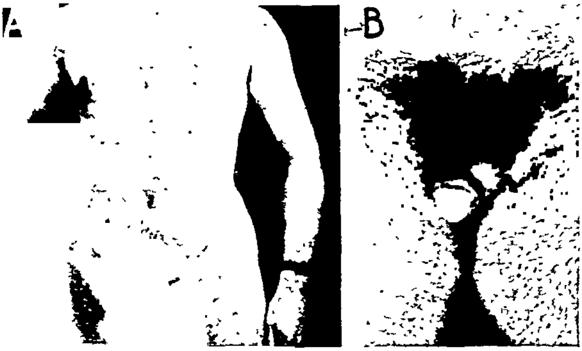

Fig. 1. *A*, photograph showing good muscular development and general contour of body. *B*, external genitalia; note distribution of hair and appearance of penis.

In view of these abnormal findings the patient's family was anxious to make a true determination of the sex so the patient was admitted to the hospital for an exploratory operation. Dr. F. X. McGovern saw the patient and confirmed the findings. On August 5, 1943, the right inguinal canal was again explored but neither testicle nor spermatic cord was present. The upper angle of the incision was enlarged so a limited exploration of the peritoneal content could be made. Near the midline a small but well formed uterus was found. On the right side a small ovary and fallopian tube were attached to the right cornu of the uterus. A gynecologic confrere, Dr. R. J. Jansen, saw the patient at this time, confirmed the above findings, and recommended a hysterectomy. On the left side of the uterus a typical vas deferens was attached, but could not be traced to the testicle. We were quite sure that testicular tissue was present as the masculine secondary sex characteristics were so evident, but did not feel justified in exploring the left inguinal canal in order to satisfy our surgical curiosity. The adrenal glands could not be palpated. In view of these findings and after careful consideration of the factors involved, it was decided to convert the individual into a male by removing the diminutive uterus and ovary. This was done and the adherent phallus freed from its attachment to the raphé (fig. 2).

pseudohermaphrodite has married, and was later proven to be a member of the opposite sex.

In the treatment of true hermaphroditism the physician is faced with a grave responsibility if an attempt is made to alter the sex pattern of the individual. In view of the fact that most of these individuals are reared as a male, they should under ordinary circumstances be brought up as a male, obviating the chance of a homosexual marriage.

Cahill states that maldevelopment of other parts of the genital tract is frequently observed in this condition and as a result of malformation, or from pressure or obstruction, evidence of urinary tract infection may develop. In other instances surgical procedures may be necessary such as amputation of the clitoris or partial removal of an accessory gonad.

Recent developments in the field of endocrine therapy may eventually effect beneficial results in both the intersexual type and the definite hermaphrodite. It was utilized by McIver, Lattimer, Engle and Yeaw, and is being carried out in the case herein presented.

REPORT OF CASE

A. L., a white individual, aged 20, was examined July 26, 1943. Since birth, lack of control of the direction of the urinary stream, cryptorchidism, and absence of the scrotum and penile urethra were observed. See figure 1.

The patient stated it was necessary to assume a sitting position to urinate because of the presence of a perineal opening. An anomalous problem was presented as the condition was a constant source of embarrassment to this patient particularly when in school. There was no evidence of menstruation nor were any cyclic emotional disturbances experienced during adolescence.

The patient's general health was good, and aside from this anomaly he had not been ill. The individual was emotionally stable, not easily excited, and enjoyed the company of boys rather than girls. A sister several years older was normal, and the parents stated there was no history of abnormal sexual development in the family. He was a well nourished and developed adult of masculine appearance, there being no excessive deposit of fat. In the lower abdomen a scar was located in the midline as well as a second one in the right inguinal region. At the age of 6 years an unsuccessful attempt had been made elsewhere to correct the cryptorchidism.

Clinically neither kidney was palpable, and no masses could be detected. The external genitalia with the exception of the phallus resembled that of a female, as two well developed labia were present. The phallus measured 4 by 7 cm; it was normal in shape, but was markedly adherent to the raphé. The glans penis was well developed, but there was no evidence of a penile urethra. The distribution of labial hair was gynecoid. The urinary meatus was located in the perineum 3 cm. anterior to the anus, and there was no evidence of a separate vaginal orifice. The contour of the body and deposit of fat were typically android, and no enlargement of the mammary glands was noted. An x-ray study revealed a male bony pelvic outlet, and the bone development was not advanced. An excretory

Following this, his fourth major operation, the patient became more masculine in appearance and attitude. He tried to enlist in the Army and later planned to study medicine, but his physical condition precluded the former, and his lack of education the latter.

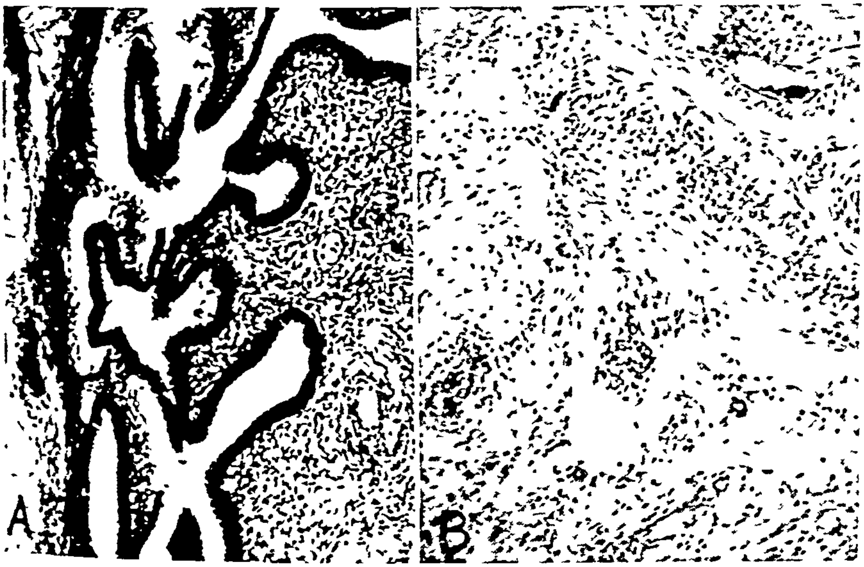

FIG. 3. *A*, uterus *B*, rete testis

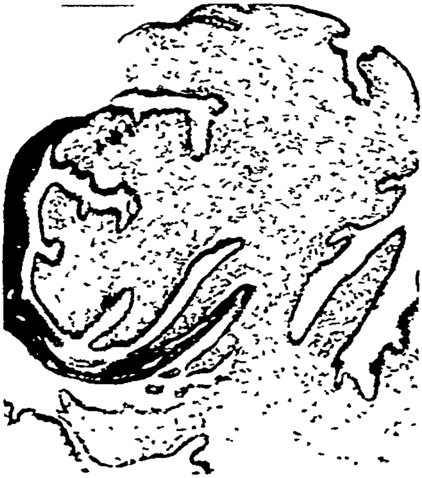

FIG 4 Fallopian tube

Owing to the fact that the patient had lost so much time from school, and had had two major operations within a short time, the parents decided to defer to a later date the plastic operation on the perineal hypospadias At that time the libido was definitely android in character, and he stated that he had normal erections, and at intervals nocturnal emissions (which is seriously doubted) The

A year later Dr. Hugh H. Young saw the patient in consultation, went over the slides and confirmed the gross and microscopic findings. He performed a cysto-urethroscopic examination, found the bladder normal but the verumontanum and prostate were absent. A rectal examination also revealed the absence of the prostate and seminal vesicles.

In the interim the patient resumed his school work, and had no symptoms other than previously observed. He was placed on testosterone propionate 10 mg. weekly in an effort to stimulate his secondary male characteristics. After taking this hormone for 16 months a definite increase in the distribution of hair was noted on the face and chest. The size of the phallus has remained about the same.

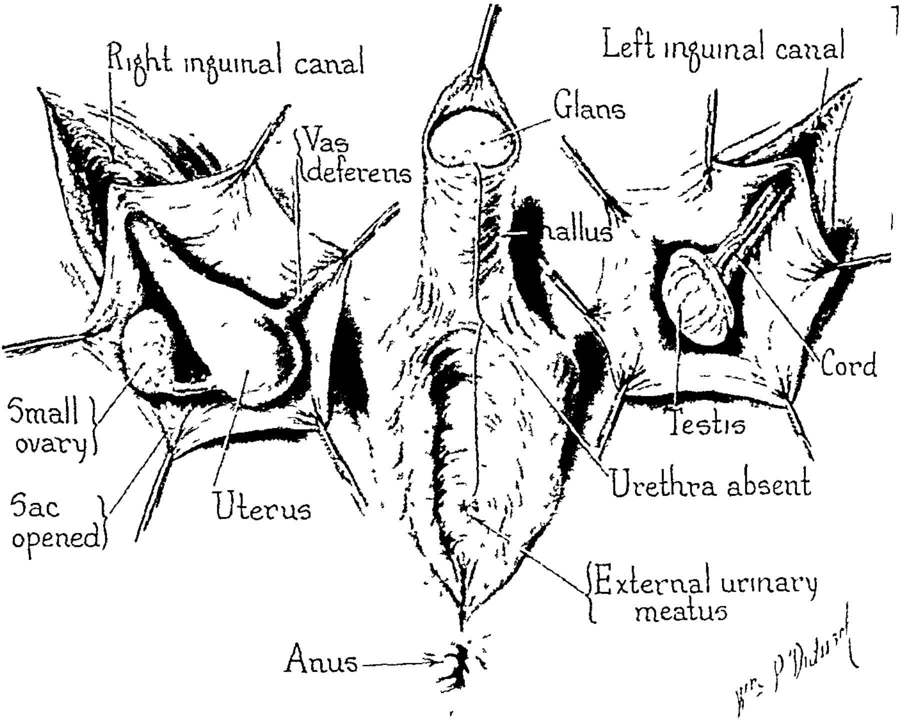

FIG. 2. Showing location of organs and their anatomical relationship

On December 12, 1944 (sixteen months later) while lifting a heavy object, sharp pain was experienced in the left inguinal region. An examination revealed a mass which on exploration proved to be a firm, small testicle attached to the spermatic cord lying free in the hernial sac. There was marked atrophy of the epididymis. It was decided to place the testicle in the left labial fold, anchoring it to the inner portion of the left thigh, following which the hernia was repaired. A pathologic study of the removed uterus, fallopian tube, ovary, and a biopsy of the testicle confirmed the presence of all of these elements. These histologic studies were made by Drs. J. W. Lindsay and T. Winship. Sections of the ovary revealed typical stroma but no graafian follicles were present (figs. 3, 4 and 5).

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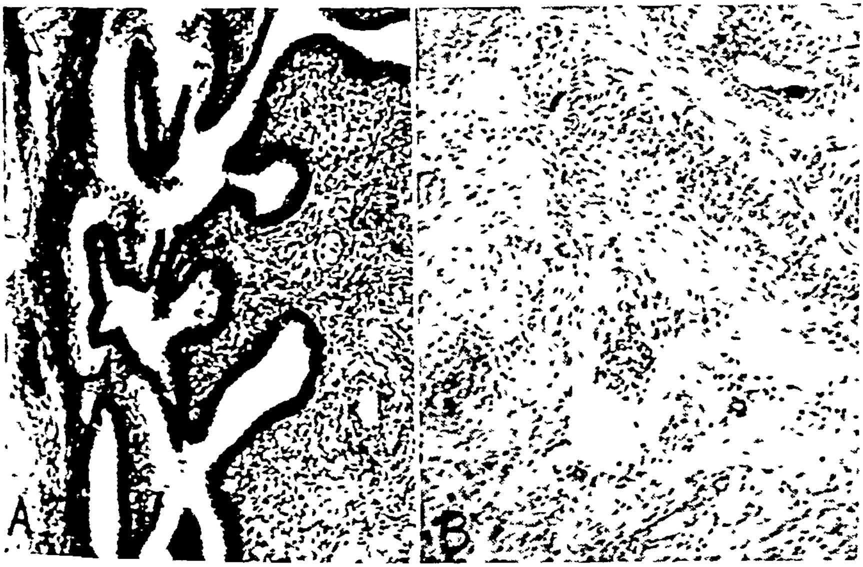

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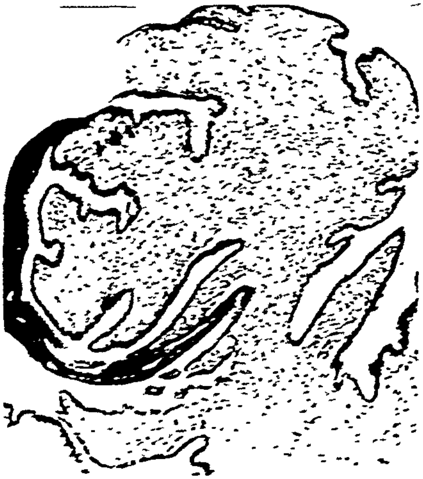

FIG. 4. Fallopian tube

Owing to the fact that the patient had lost so much time from school, and had had two major operations within a short time, the parents decided to defer to a later date the plastic operation on the perineal hypospadias. At that time the libido was definitely android in character, and he stated that he had normal erections, and at intervals nocturnal emissions (which is seriously doubted). The patient was seen at regular intervals until March 13, 1948, when Dr. Alfred J. Suraci was consulted and performed the reconstructive procedures necessary for the formation of a penile urethra and repair of the perineal hypospadias.

Hypospadias is generally classified as glandular, penile, penoscrotal or perineal, and is on the ventral surface of the phallus. Fortunately, the majority are located in the distal portion of the urethra and rarely produce obstruction. In the perineal type normal micturition can only be performed in a sitting position which is exceedingly embarrassing to the patient, and often leads to local irritation.

Hinman states: "A study of comparative anatomy shows that hypospadias is a hermaphroditic condition, a tendency of the sinus urogenitalis of the male to develop toward the female side and not an inhibition of growth". The majority of urogenital anomalies are fundamentally hermaphroditic depending on which sex tendency is stimulated or inhibited. For these reasons some form of restoration is usually indicated. At this time there is no need to discuss the various techniques or theories that have been presented in the distant or more recent past by surgeons employing various reconstructive procedures. Suffice to record that quite a number of methods have been proposed, one of which, a modification of the plastic procedure described by Blair, Brown and Hamm offers, in our opinion, less postoperative contracture than do other procedures in which free skin grafts are utilized. Despite statements to the contrary, one of us (A. J. S.) has observed several instances of secondary contracture following free skin graft operations on the penis.

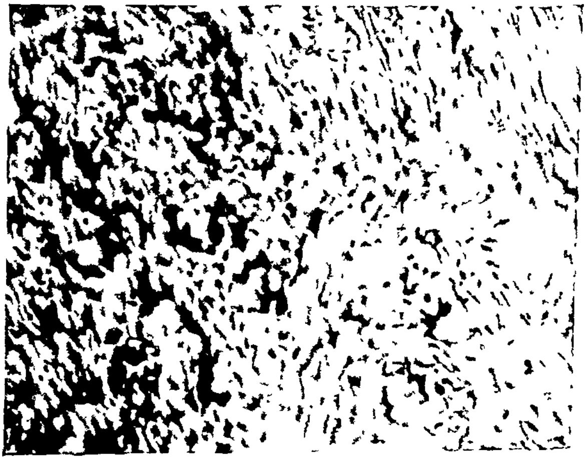

FIG. 5. Ovary

In the repair of perineal hypospasias attention must be paid to certain basic principles of plastic reconstruction to obtain the best results. These include: a carefully considered preoperative plan of procedure, outlining and measuring penile and scrotal tissue to secure adequate flaps, proper choice of time for transposition of these flaps, correction of chordee, perineal or suprapubic diversion of urine, use of tissue closely resembling the recipient area functionally, restoration of a functional urethra, prevention of one suture line being directly superimposed on the other in a straight line and insurance of adequate blood supply to the newly formed flaps. In the event any change in the initial operative procedure becomes necessary, an alternate plan should be anticipated. The width of the flaps to form the urethra should be carefully measured and should be 1½ to 2 times the circumference of the catheter or prosthesis utilized (fig. 6, *A*). These conditions were satisfied in this case, and the tissues of the penis and labia utilized for the restoration. The original operation was modified by one of us (A. J. S.) as it was found that the right side of the bifid scrotum contained more redundant tissue than the left owing to the presence of the transposed testicle on the left side, therefore, most of the restoration, migration and rotation of flaps were performed on the right side.

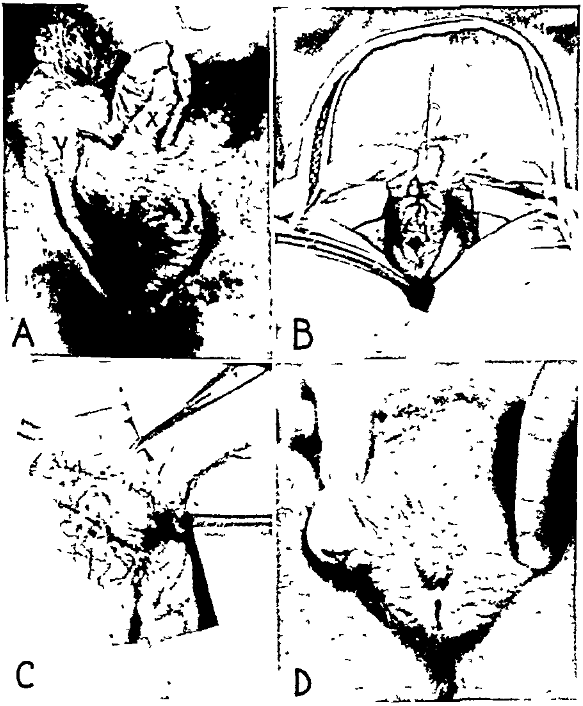

FIG. 6 *A*, flap outlined in India ink X will form penile urethra whereas Y will be elevated primarily to receive raw surface of penile shaft *B*, formation of fossa navicularis *C*, showing all sutures in place Note bed sutures to prevent hematoma formation and dead space. *D*, appearance 3 weeks after operation.

On May 13, 1948, the first step in the restoration was the establishment of a new fossa navicularis (fig. 6,B). Six weeks later the new urethra was formed around a size 28F catheter. Repair of the urethra was stopped at the base of the penis where the normal bend occurs, for if an attempt is made to lengthen the channel at this point the wound usually breaks down.

A flap was then formed on the right side of the bifid scrotum and the shaft of the penis buried into this flap, suturing the free edge of the flap to the right border of the penis approximating the raw surfaces. This flap was allowed to heal and remain in this position for three months (fig. 6, *C* and *D*).

On August 12, 1948 the second major reconstructive procedure was undertaken after a preliminary suprapubic cystostomy had been performed to divert the urinary stream. The advisability of diverting the urinary stream through the perineum was considered, but the proximity of the urinary meatus to the anus and disposition of the vestigial vagina did not lend itself to this type of drainage. By freeing the scrotal flap from its attachment to the penile shaft it was com-

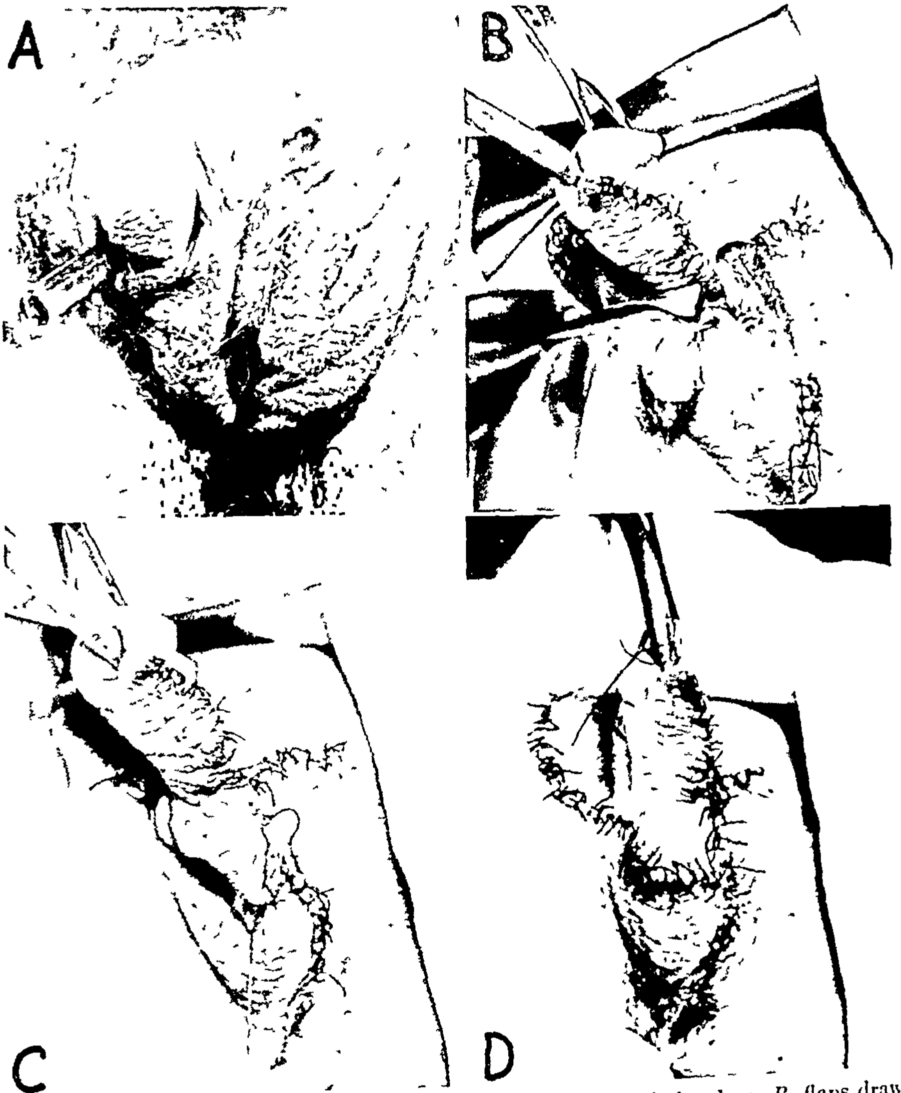

FIG. 7. *A*, urethra in shaft of penis completed and prosthesis in place *B*, flaps drawn together to show plan of closure. *C*, lengthened flap rotated into position, additional closure accomplished *D*, final closure, planned and executed to eliminate superimposed suture lines for better closure and utilization of tissue from penis and scrotum for restoration, due to its elasticity, particularly in adult life

pletely mobilized and the second or proximal portion of the urethra formed over the 28F catheter. Closure of the left border of the penile shaft defect was accomplished by rotating the previously formed flap toward the midline. The flap was rotated in position and wound edges approximated on the left side. Final closure was executed in such a manner as to eliminate superimposed suture lines, thus lessening the probability of postoperative contracture and interference with normal erection of the penis. See figures 7 and 8.

The final result was very satisfactory. The prosthesis was removed, the newly formed urethra dilated, and an indwelling Foley catheter passed to the bladder to promote healing of the suprapubic incision. The catheter was removed on the tenth day, and for the first time the patient was able to void normally through the urethra.

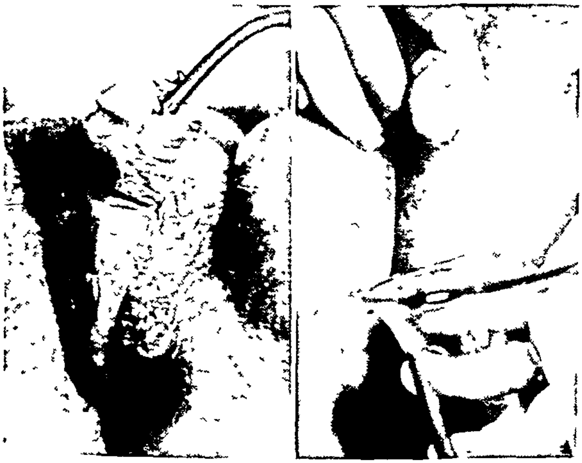

FIG. 8. *A*, postoperative appearance showing completely healed, rotated flap and indwelling Foley catheter. *B*, final result.

The administration of testosterone propionate has been continued since the original operation in 1943. The transplanted testicle has assumed a firm texture, and is larger than when first transplanted. The ejaculate, which was scanty in amount and obtained by masturbation, revealed no spermatozoa, lipoid granules or corpora amylacea.

CONCLUSIONS

A case of true bisexuality is reported and verified by positive microscopic findings.

Unilateral cryptorchidism was found. The external genitals were gynecoid, the urethra in the perineum, and the external vaginal orifice absent.

Exploration of the abdominal contents disclosed a well formed uterus, tube and ovary on the right side. A small testicle and cord were later found on the left side, and a vas deferens was attached to the left cornu of the uterus.

The phallus presented a normal glans which was well formed, devoid of urethra, and did not represent an enlarged clitoris.

Androgen, estrogen and ketosteroid assays revealed a preponderance of female hormone.

Testosterone propionate injections are being utilized, and have accentuated the secondary sex characteristics.

Complications observed in connection with hermaphroditism include bifid or cleft scrotum, congenital hernia, chordee, cryptorchidism, and absence of the testicle.

Careful surgical planning with meticulous execution of the procedure has considerable to offer these unfortunate individuals, aiding them to live a relatively normal life both physically and psychologically.

This patient is highly pleased with the surgical results obtained and has expressed great appreciation, stating that he is happier than he has ever been during his adult life.

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REFERENCES

Blair, V. P., Brown, J. B. and Hamm, W. G.: The correction of scrotal hypospadias and of epispadias. Surg., Gynec. & Obst., **57**: 646–653, 1933.

Hinman, F.: The Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1935.

Stirling, W. C.: Report of a case of true hermaphroditism; discussion of 37 cases previously reported. J. Urol., **56**: 720–724, 1946.

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INTESTINAL GAS DURING PYELOGRAPHY

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From the Departments of Surgery and Urology of Northwestern University Medical School, Chicago, Ill.

To a group interested in the general problem of gastro-intestinal gas, the occurrence of meteorism during pyelography is of special concern. Here is a situation in which intestinal gas is often seen to be considerably increased in the last pyelogram as compared to the first, a period of roughly 30 to 60 minutes. Such accumulations in a relatively short period of time offer the possibility of learning how the gas develops or where it comes from.

In a previous investigation on the mechanisms of acute abdominal distention, Morris, Ivy and Maddock discussed the rapidity with which acute gastric dilatation can occur as a reflex phenomenon associated with a great variety of diseases, and how air can be ingested by air-suckers and esophageal speech experts. They showed how the air-suckers can relax the superior esophageal sphincter and then by attempting to breath against a closed glottis inspire air into the esophagus whence it can be belched back or allowed to pass into the stomach. The ingestion method taught to the esophageal speech subject is essentially the same, and words are formed with the eructated air. If the sphincter, in those not able to relax it voluntarily, is opened by intubation with a small rubber tube, air can similarly be ingested by inspiratory efforts. Thus there are ways of having external air pass into the esophagus without swallowing.

In general, the impression is held by radiologists, urologists and others that the gas seen during pyelography, just as in other flatuosities, is "swallowed" or external air, but different theories have been offered by Oppenheimer and Begg.

In 1940, Oppenheimer, noting that during retrograde pyelography excessively large amounts of gastro-intestinal gas often appeared when that procedure produced pain, studied the relationship between pain and gaseous distention. He found that gaseous distention was not observed in 82 instances of severe pain occurring with fractures of the extremities and spine, gonococcal arthritis, sciatica, lumbago, toothache, trigeminal neuralgia, herpes zoster and dislocations. However, in many cases of renal colic, biliary colic, duodenal ulcer, acute appendicitis and salpingitis, the type of gaseous distention was identical with that found during retrograde pyelography. In 14 patients with urinary disease in whom excretory urography was done with complete absence of pain, gaseous distention developed. These findings led Oppenheimer to believe that pain in itself was not responsible for the appearance of gas in the bowel, but that some abdominal diseases may cause both pain and gaseous distention. A variable not mentioned is the individual reaction of patients, a factor appearing of considerable importance in this study.

Oppenheimer further observed roentgenographically in man that ureteral catheterization and distention of the renal pelvis with fluid or oxygen was fol-

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Read at annual meeting, American Urological Association, Washington. D. C., June 1, 1950.

lowed by rapid overfilling of the stomach, small intestines and colon with gas. He stated that the large amounts seen within a few minutes could not possibly be due to abnormal fermentation or diffusion from the blood stream, and offered the thesis that the small amount of gas always present in the intestines quickly expanded to fill the intestines when they became atonic due to inhibitory reflexes which arise from renal or biliary colic, pyelography, etc.

Oppenheimer's observations are excellent, but his thesis is not plausible for the reason that a given amount of gas cannot expand into a larger space without a reduction in pressure, and the soft intestinal tube and flexible abdominal wall would collapse under reduced pressure. It has been shown that intestinal gas pressure is close to atmospheric pressure except during active peristalsis.

In 1948, Begg, writing on a rational theory of intestinal distention and its application to urology, contended that gas pains and distention may be completely obviated if nothing whatever is given by mouth or rectum during the inevitable postoperative nonperistaltic period. He offered the following reasons for not believing that distention was due to air swallowed during and after the operation: 1) The theory is inapplicable to distention accompanying spinal lesions, lightning stroke, renal colic or anuria, unless one is to suppose that the victims suddenly become addicts to aerophagy. 2) It is incompatible with the observed fact that postoperative patients if given no fluid do not distend no matter what air they may have swallowed. He further stated that if it were contended that the air was swallowed with the fluid, it would be difficult to imagine that a single drink would initiate progressive and increasing distention such as he had observed.

Since the swallowed air theory was unsatisfactory and the role of food fermentation disproved, Begg considered the only remaining possibility to be gas derived from the blood, it being available to the bowel by "intestinal respiration" and absorbed when in excess. Knowing that the passage of nitrogen to the bowel and back to the blood depends on the physical laws of diffusion of gas, Begg believed that any factor which, when the dynamic function was in abeyance, reduced the tonus, increased the potential capacity of the bowel lumen and allowed the inflow of gas. He further believed that food and fluids reaching the stomach during the postoperative refractory period caused this organ to contract on its contents, thus leading to a reflex reduction in tone of the intestines which enabled the blood gases to flow in to fill the increased space in the lumen. He called attention to the large increase in intestinal gas when an ureteral catheter was passed, and similarly quoted the quick influx of gas into the bowel following the injection of uroselectan as further evidence of the theory of rapid diffusion of nitrogen into the bowel when the requisite conditions are present.

The authors believe that when neither food nor fluids are given to postoperative patients the possibility of gaseous distention is reduced but certainly not entirely eliminated, since they have seen gastro-intestinal distention develop in patients receiving nothing by mouth. As to Begg's opinion that swallowed air cannot be the main source of gastro-intestinal gas unless "the victims become sudden addicts to aerophagy," the authors consider that this is exactly what takes place in many instances, if one uses the term aerophagy in a broad sense covering the rapid ingestion of air.

The purpose of this study was to prove that external air is the main source of the gas in meteorism during pyelography, the method being the prevention of an increase in the intestinal gas by keeping the stomach empty of air during that time. Before presenting the experiment, the question of how fast gas could pass from the stomach and through the small intestines should be briefly discussed. Gas is usually not thought of as passing along any faster than food, but it actually does, Magnusson being the first to study this point in 1931. He also dismissed gas formation from intestinal decomposition and diffusion from the blood as possible sources of meteorism in pyelography, and contended that the main bulk of the gas consisted of air that had passed down the esophagus. Magnusson's important point was that the "swallowed air" must pass out of the stomach and through the small intestine rapidly in order to obscure the region of the kidneys, ureters and bladder. To confirm his supposition, he filled the colon of normal adult subjects with an opaque enema so that air coming into the cecum could be easily seen. The subjects were then turned on their left side to place the pylorus upward and air was injected into their stomach. It reach the cecum in an average of 10 minutes and passed through the anus in 30 minutes.

In 1949, Maddock, Bell and Tremaine made a further investigation of this rapid air passage through the gastro-intestinal tract, using as subjects young male medical students. An initial scout film of the abdomen showed the amount of gastro-intestinal gas present. A Levine tube was then introduced into the middle esophagus and through it known volumes of air were allowed to enter the stomach. Frequent roentgenograms showed its progress, and flatus was collected. The results obtained were essentially the same as Magnusson's. It took an average of 14.6 minutes for the air to reach the cecum, and 24.1 minutes for the appearance of the first flatus. The average volume of flatus collected was 970.8 cc in 83.6 minutes, which was reasonably close to the average of 1133 cc air entering the stomach.

It is apparent from these rapid passage figures that when on routine roentgenograms one sees gas in the stomach, small intestines and colon, it need not be thought of as originating in each of these structures, but rather as external air that came down the esophagus and quickly passed along the line. As stated before, the authors consider the rapid accumulation of gas in the intestines during pyelography as an excellent example of the aspiration and quick transit of external air through the alimentary tract.

The study of gastro-intestinal gas in patients undergoing excretory or retrograde pyelography is a very satisfactory experiment in many respects. The time period is short, approximately an hour, and the increased amount of gas seen in many routine pyelographies is sufficient in amount to be measurable. If "acute aerophagy" is to develop the stage is well set, since the process is almost certainly a nervous, reflex phenomenon and the patient undergoes several strange and uncomfortable procedures which may easily arouse fears and apprehension. Also, during retrograde pyelography the urethra, bladder, ureters and renal pelvis are stimulated, conditions often observed to be associated with increased intestinal gas, even though pain is absent.

Method. For the study the patients were prepared in the usual manner for pyelography.* Fluids were restricted for several hours before the retrograde, but not before the excretory study, and no breakfast was given. A Wangensteen tube was passed to the stomach a few minutes before the initial pyelogram and continuous suction started with water siphonage. The total amount of small increments of gas aspirated was determined by water displacement in a graduated collecting system. To begin with, the stomach was emptied of fluid and air by aspiration and the amount of intestinal gas was shown by the initial pyelogram. The patients were asked not to swallow, and most of them did so infrequently. A careful record was kept of the return of gas as related to the procedures of the pyelography, to swallowing movements, to apprehension or pain or other complaints of the patient, and to changes in the rate and depth of respirations from any cause. The effectiveness of the gastric suction in keeping the stomach free of air was determined by observations as to whether the tube was open and working, and by the roentgenograms.

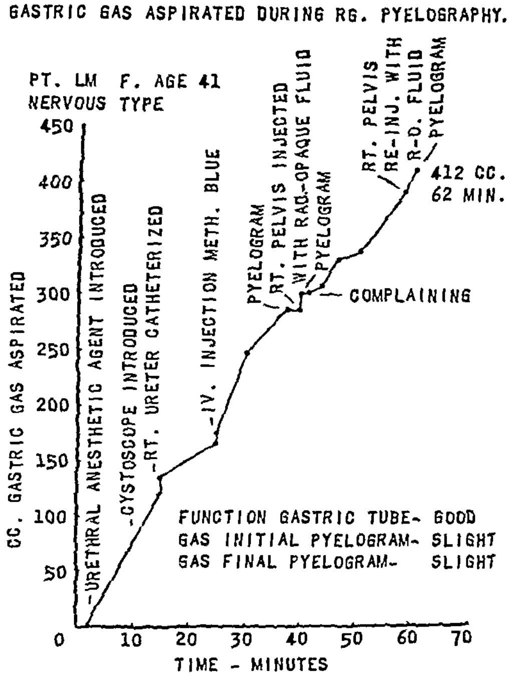

FIG. 1. Graphic record of gastric gas aspirated during retrograde pyelography from a nervous patient, L.M. Gaseous return sharply increased when right ureter was catheterized, methylene blue was injected intravenously and right renal pelvis was injected with radio-opaque fluid. Respiratory rate and depth increased at these times. Even roentgenographic exposures elicited a response.

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* This part of the study was assisted by Dr. Earl Barth, associate professor of radiology, Northwestern University Medical School.

Results. Figure 1 shows a typical response observed in a nervous patient undergoing retrograde pyelography. A total of 412 cc gas was aspirated from the stomach in 62 minutes, roughly 7 cc per minute. The process seemed definitely related to deeper and irregular respirations as nervous responses associated with the different procedures done, such as the passage of the cystoscope, etc. Of special interest was the fact that when the stomach was kept empty of air there was no increase in intestinal gas from the initial to the final pyelogram, as shown in figure 2.

Figure 3 shows a typical result in a nervous patient undergoing excretory urography. This man returned a total of 1345 cc of gastric gas in 64 minutes, approximately 20 cc per minute. This was the largest amount obtained from the group studied. This man swallowed infrequently. He complained about everything, the lower abdominal pressure pad was too tight, his respirations were deep and irregular, and a steady stream of air was aspirated from the stomach during the whole period.

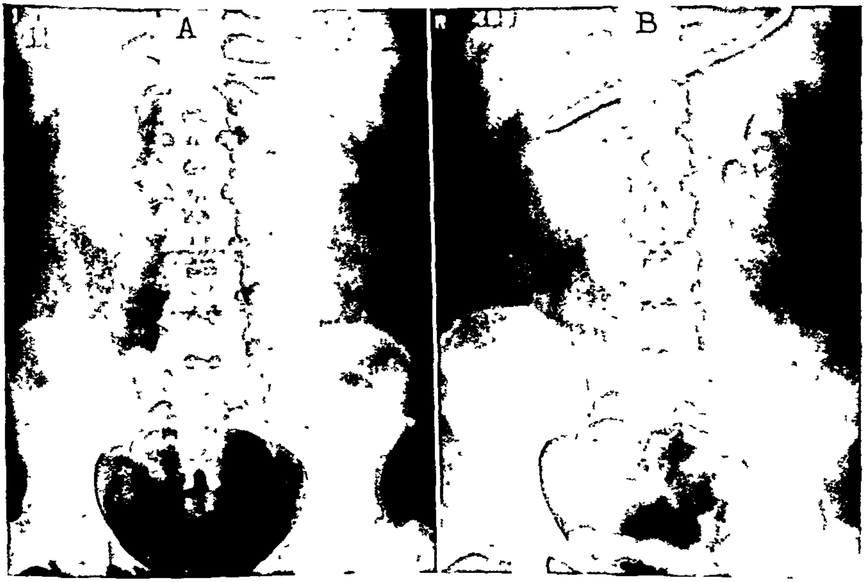

FIG 2 Roentgenogram of patient L.M. *A*, immediately after left ureteral catheter was inserted. *B*, 62 minutes later, during which time 412 cc gastric gas had been aspirated. The stomach was kept free of air and consequently there was no increase in intestinal gas from the early *A* to the final roentgenogram *B*.

The data from all the patients are summarized in table 1, and from them the following pertinent comments are offered.

The time period of pyelogram studied varied from 35 to 68 minutes, and the volumes of gastric gas aspirated varied from 45 to 1345 cc. Neither the age nor the sex of the patients appeared to influence the findings. The outstanding fact was that for those subjects in whom the stomach was kept empty of air by continuous suction through the gastric tube there was no increase in the amount of intestinal gas during the period from the initial to the final pyelogram.

would not be true if diffusion or fermentation were important sources of intestinal gas in these cases. The evidence is, therefore, that the gas seen in routine pyelograms comes from external air. An analysis of the gastric gas aspirated from patient J. M. during pyelography showed carbon dioxide 1.70 per cent, oxygen 19.53 per cent, and nitrogen 78.80 per cent, which is close enough to the concentrations of external air to indicate the latter to be its source.

Indirect evidence that the increase in intestinal gas seen during pyelography comes through the stomach was furnished by the 5 patients in whom it was known that the gastric tube did not function well (recorded as poor in table 1) in maintaining continuous suction. In 4 of the 5, intestinal gas was increased from the initial to the final pyelograms as a result of some air passing through the pylorus.

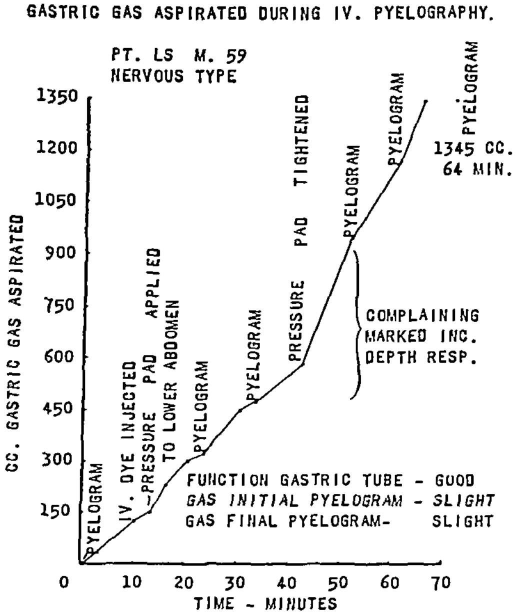

FIG. 3. Graphic record of largest amount of gastric gas aspirated during a pyelography. L.S. was very nervous and apprehensive and stimuli from the various procedures carried out resulted in a marked increase in the rate and depth of respirations. Gaseous return at these times was increased. Discomfort from the lower abdominal pressure pad was the most disturbing factor.

An extremely important observation was that three times as much gas was aspirated from the stomachs of the nervous patients as from the calm ones. Such a nervous factor has been commented on in many observations on gaseous abdominal distention. The averages of table 1 show this distinctly, with no material variation whether the patients were undergoing excretory or retrograde pyelography. In individual experiments we noted that more gas was aspirated during the episodes of deeper, irregular respirations when the patient was distressed by some part of the procedure, and that the nervous patients were more easily distressed and had longer periods of deeper breathing than the calm ones. Two patients, E. S. and R. J., were addicted to frequent swallowing which became pronounced during disturbed periods and was likely responsible for some of the gas collected. When requested, the others were able to control the act of swallowing and in them this occurred too infrequently to account for any appreciable portion of the gas obtained. The volume aspirated following a single swallow varied from 0.3 to 5.0 cc, averaging from 2 to 3 cc, while the amount of gas returned with one deep breath varied from 0 to 5 cc, with an average of 1 to 2 cc. A respiratory rate of 20 per minute gave plenty of opportunity to take in considerable air.

TABLE 1. *Summary of data on gastric gas aspirated from patients undergoing pyelography*

SUBJECT	SEX	AGE	REACTION OF PATIENT	GASTRIC GAS ASPIRATION		ESTIMATION OF INTESTINAL GAS ON PYELOGRAMS		FUNCTION GASTRIC TUBE
				Minutes	CC	Initial	Final	
Intravenous Procedure								
J. W.	M	53	Calm	61	100	Slight	Slight	Good
S. B.	F	68	Calm	62	105	Slight	Slight	Good
C. B.	F	44	Calm	52	195	Slight	Slight	Good
J. A.	M	51	Calm	46	45	Slight	Moderate	Poor
C. S.	F	42	Calm	61	165	Moderate	Moderate	Poor
F. S.	F	66	Nervous	37	165	Slight	Slight	Good
M. E.	F	53	Nervous	35	195	Slight	Slight	Good
R. L.	M	15	Nervous	44	200	Slight	Slight	Good
L. W.	F	43	Nervous	41	240	Slight	Slight	Good
L. S.	M	59	Nervous	64	1,345	Slight	Slight	Good
P. R.	F	66	Nervous	68	280	Moderate	Moderate	Fair
R. J.	M	23	Nervous	53	415	Moderate	Moderate	Fair
R. B.	F	18	Nervous	48	75	Slight	Moderate	Poor
E. S.	F	66	Nervous	50	175	Slight	Moderate	Poor
Average calm group				56	122			
Average nervous group				49	343			
Retrograde Procedure								
D. B.	F	38	Calm	60	55	Slight	Slight	Good
M. R.	F	47	Calm	56	115	Slight	Slight	Good
W. B.	F	72	Nervous	40	225	Slight	Slight	Good
L. M.	F	41	Nervous	62	412	Slight	Slight	Good
P. D.	F	66	Nervous	45	90	Slight	Moderate	Poor
Average calm group				58	85			
Average nervous group				49	242			

Important findings. 1) When the stomach was kept free of air by continuous suction through the gastric tube there was no increase in intestinal gas from the initial to the final pyelogram. 2) Approximately three times more air was aspirated from the stomachs of nervous patients than from the calm ones.

SUMMARY

Patients undergoing pyelography frequently show some meteorism and therefore offer an excellent opportunity for studying the rapid accumulation of intestinal gas. In this investigation continuous gastric suction removed considerable volumes of air from the stomachs of patients undergoing pyelography, and no increase in intestinal gas occurred when the stomach was kept empty. An analysis of the gastric gas removed was approximately that of external air. This is direct evidence that external air is the major source of gastro-intestinal gas accumulating during pyelography.

Another important observation was that in the nervous patients undergoing pyelography there was three times as much air aspirated from their stomachs as from the calm patients. Ordinary swallowing movements were infrequent and did not account for much of the ingested air. The factors appearing responsible for the nervous manifestations were intravenous injections, the passage of the cystoscope and ureteral catheters, the introduction of fluid into renal pelves, and the discomfort of the lower abdominal pressure pad. These stimuli resulted in irregular and deeper respirations, and during these periods the gas return was greatest.

Thus nervous reactions appear to be an important factor in meteorism during pyelography and this finding is in accord with the opinion that many forms of flatulence are a nervous manifestation. Acute gastric dilatation has been found associated with such a wide variety of diseases that it must be brought about by a reflex nervous mechanism. Typical aerophagics are nervous, worried, irritable, distracted and hyperactive people. The authors believe that patients under many conditions become temporary aerophagics of varying degree, and that the stimulus may be entirely nervous without apparent organic disease, or it may be associated with an organic disease or injury and its treatment.

The preparation of patients for pyelography by enemas and cathartics has not been too successful in eliminating meteorism because the obscuring gas is ingested shortly before or during the pyelogram and no form of prior cleansing suffices. It is a bit too drastic to use continuous gastric suction on all patients undergoing pyelography, but sedatives to allay fear and apprehension are suggested as part of the preliminary preparation.

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REFERENCES

Begg, R. C.: A rational theory of intestinal distention and its urological application. J. Urol., 59: 358, 1948.

Maddock, W. G., Bell, J. L. and Tremaine, M. J.: Gastro-intestinal gas: Observations on belching; during anesthesia, operations and pyelography; and rapid passage of gas. Ann. Surg., 130: 512–537, 1949.

Magnusson, W.: Meteorism in pyelography and on the passage of gas through the small intestine. Acta. Radiol., 12: 552, 1931.

Morris, C. R., Ivy, A. C. and Maddock, W. G.: Mechanism of acute abdominal distention. Arch. Surg., 55: 101–124, 1947.

Oppenheimer, A.: Gas in the bowels. Surg., Gynec. & Obst., 70: 105, 1940.

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DISCUSSION

DR. H. W. BRUSKOWITZ (Madison, Wis.): Doctors Tremaine, Maddock, and O'Conor are to be highly commended for their efforts to explain and to avoid a condition which is a potential occurrence in every patient subjected to excretory urography. The appearance and the distribution of intestinal gas during the procedure may be of such a pattern as to render the urograms worthless from a diagnostic standpoint.

My associate and I, in the clinical studies which we have been making at the Jackson Clinic, have been vitally interested in the problem of intestinal gas, but we have attempted to avoid the complication by endeavoring to produce a concentration of the contrast medium in the urine to the point where intestinal gas will not obscure portions of the tract. In other words, we have attempted to approach medium concentration similar to retrograde pyelography, where intestinal gas is no particular deterrent to the procedure, and rarely does the distribution render the retrograde pyelogram undiagnostic.

We have recognized the medical shock incident to the injection of the iodine solution as the inciting factor in the production and the distribution of intestinal gas, whatever may be its source, and attempted to minimize it by the use of sedation by barbiturates administered an hour or more previous to the injection of the medium.

Unfortunately we kept no data as to the patients' psychic reactions during the procedure, but we distinctly recall that several of them slept through the period of time required for the exposures. Nor in reviewing the films did we note data especially concerning intestinal gas, but our impression on the whole was that there was little difference in this group from other groups.

As the authors have stated, they believe that the accumulation of gas in the intestine during pyelography was an example of aspiration and quick transit of external air through the upper alimentary tract, and their studies have certainly confirmed this point. One must marvel at the rapidity with which air may be aspirated and appear in the cecum and large bowel, which in their experience occurred on an average of 14.6 minutes. In reviewing the films in the studies which we have been making, we have found in several instances that there was extensive meteorism on the five minute film.

The most important findings in their studies are that approximately three times more air was aspirated from the stomachs of nervous patients than from the calm ones and that when the stomach was kept free of air by continuous suction through a gastric tube there was no increase in intestinal gas from the initial to the final pyelograms. It was on the basis of these findings that the authors concluded that pyelography did not produce atony of the bowel and consequent expansion of gas already present, as suggested by Oppenheimer, or rapid diffusion of nitrogen into the bowel as theorized by Begg.

I should like to point out that, on the average, 100 cc more of air was aspirated on the patients undergoing excretory urography, as compared to those undergoing retrograde pyelography. In the data which were available to me it was not clear whether or not this latter group of patients received precystoscopic sedation and analgesics. One would certainly expect to find as the result of painful manipulations of the urinary tract that the patients undergoing these examinations would swallow more air than those having excretory urography.

While the quantity of air aspirated in their cases has not been unusually large except in the one instance, and if gastric suction is to be used at times as a part of the procedure of pyelography, I can see, as the authors have pointed out, that unless it functions perfectly, more intestinal disturbance may occur from aspirated air than without its use. After I was asked to discuss this paper, I have made it a point to visit most of the patients in our hospital who have a gastric suction tube in place for whatever reason, and the vast majority of them reported a more or less constant desire to swallow during at least the first 48 hours that the tube was in place.

We are all aware of the fact that meteorism is practically an invariable accompaniment of renal and ureteral colic and that some disturbances in the motor function of the gastro-intestinal tract must occur, because each of us sees annually one or several patients whose only complaints are referable to the gastro-intestinal tract. Yet these patients, in whom the most careful history will reveal no symptoms other than those referable to the gastro-intestinal tract, and whose gastro-intestinal tracts are normal according to our accepted methods of examination, are promptly and completely relieved by the removal of a renal or ureteral calculus.

We are grateful to the authors for their efforts, and they have indicated that they propose to continue their studies. I would like to suggest that as a part of their problem they study the relation of the dynamics of the gastro-intestinal tract to the urinary tract and vice versa. The enterorenal syndrome, so called by some, and so poorly understood, may well fit into the picture of the problem on which they are working.

Dr. Myron J. Tremaine (Chicago, Ill.): The suggestion made by Dr. Bruskewitz relative to studying the dynamics of the gastro-intestinal tract in comparison with the urinary tract is a good one.

I believe it would be well to minimize the nervous reactions in patients undergoing pyelography. This would tend to minimize the amount of air aspirated and thereby result in more satisfactory pyelograms.

None of the patients on whom our observations were made received sedation prior to pyelography. We believed that that would introduce a factor which would make it more difficult to interpret the result.

The presence of the gastric tube, of course, introduced an abnormal factor and possibly influenced the result obtained in a few patients.

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USE OF ANTIHISTAMINE DRUG PROPHYLAXIS AGAINST DIODRAST REACTIONS

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A potential hazard exists during the performance of every excretory urogram. This danger takes variable forms ranging from transient nausea and peculiar gustatory complaints to laryngospasm with respiratory difficulties and even shock terminating fatally. Many investigators of this problem have concluded that these undesirable responses are allergic reactions. It is this conclusion which has constituted the premise of our earlier and present studies to determine the efficacy of antihistamine drug prophylaxis against reactions associated with the injection of contrast medium in excretory urography.[1]

Diodrast N.N.R. or iodopyracet injection (the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) and neo-iopax (the disodium salt of N-methyl-3,5-diiodo-chelidamic acid) are two of the most widely used drugs in excretory urography. Diodrast solution is of 35 per cent concentration, the iodine content being approximately 49 per cent. Neo-iopax solution is of 50 per cent and 75 per cent concentration and contains 51.5 per cent of iodine in close organic combination. The reactions associated with these drugs are thought to be caused either by their iodine content or by another substance formed subsequent to the entrance of the drugs into the circulation. Two proposals employed widely as prophylactic precautions are the use of sensitivity tests before administration of the dye and cautious consideration of patients who present positive allergic histories (i.e., allergic bronchial asthma, drug allergy, hives, hay fever, etc.). The significance of these inquiries is clearly demonstrated in the clinical observations of Alyea and Haines.[2] These investigators studied the incidence of anaphylactic reactions of 1675 patients who had been skin-tested (Naterman's intradermal test) with diodrast prior to excretory urography. They noted 4 times as many reactions in patients with previously noted positive intradermal tests as in those with negative cutaneous reactions. A further important observation was made in the group with positive allergic histories wherein the incidence of general reactions was 70 per cent in patients with positive skin tests as contrasted with 13.6 per cent in those with negative intradermal test findings.

Whether or not one subscribes to the foregoing findings is secondary to the recognition that the dangers of excretory urography are real as well as potential.

Deaths, directly attributed to the intravenous injection of diodrast, have been reported by Pendergrass,[3] Goldburgh and Baer,[4] Crane,[5] and Dolan.[6]

Read at annual meeting, Southeastern Section, American Urological Association, Gulfport, Miss., February 4, 1950.

[1] Getzoff, P. L.: New Orleans Med. & Surg. J., 101: 22, 1948.

[2] Alyea, E. P. and Haines, C. E.: J. A. M. A., 135: 25, 1947.

[3] Pendergrass, E. P., Chamberlin, G. W., Godfrey, E. W. and Burdick, E. D.: Am. J. Roentgenol., 48: 741, 1942.

[4] Goldburgh, H. L. and Baer, S.: J. A. M. A., 118: 1051, 1942.

[5] Crane, J. J.: J. Urol., 42: 745, 1939.

[6] Dolan, L. P.: J. A. M. A., 114: 138, 1940.

Deaths following the administration of neo-iopax have been reported by Daut and Dunn,[7] French and Blocke,[8] and in the medico-legal column of the *British Medical Journal.*[9]

The successful results obtained by allergists and internists in the treatment and prevention of various allergic states with antihistaminic preparations have been universally recognized. The similar use of a histamine antagonist as a prophylactic agent against the allergic reactions attending intravenous pyelography has appeared justifiable.

This report includes our observations with the use of antihistaminic drugs in the preparation of 211 patients for excretory urography. The incidence of positive conjunctival and intradermal test reaction is tabulated as follows:

Entire group—211 patients
  Positive sensitivity test reactions, 33 patients (16 per cent)
Positive allergic histories, 70 patients
  Positive sensitivity test reactions, 29 patients (41 per cent)
Negative allergic histories, 141 patients
  Positive sensitivity test reactions, 4 patients (3 per cent)

The following routine was utilized in the preparation of these patients for excretory urography.

1. On the day prior to the urographic study, a history of any of the clinical allergic manifestations is obtained. Conjunctiva and intradermal skin tests for sensitivity to diodrast are performed.

2. Nothing by mouth after the evening meal until the urographic studies are completed the following morning. (Exception: See paragraph 4.)

3. Purgation at bedtime.

4. Approximately one hour before the urograms are to be made, the patient is given an antihistamine drug according to the following routine:

a. Pyribenzamine* 50–100 mg. (depending on size and age) to the patients with negative allergic histories and negative sensitivity test reactions, hereafter in this paper referred to as the control group. (Drug is taken by mouth with one-half glass of water.) b. Pyribenazmine, 200 mg., is given to all other patients.

5. The contrast medium is injected intravenously in the following manner. One cubic centimeter is injected very slowly with a tuberculin syringe. Wait 5 minutes. If there is no reaction, complete the injection slowly with a constant eye on the patient. The appearance of any allergic manifestations is a signal for immediate discontinuation of the injection and the administration of epinephrine or ephedrine. The patient is observed thereafter until all evidence of danger has apparently disappeared.

The exclusive use of pyribenzamine in this series was not based on the belief that this drug is the best of the available histamine antagonists. The drug was employed early in this investigation and its use was continued for the sake of being consistent.

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[7] Daut, R. V., and Dunn, J. H.: J. Urol., 61: 1094, 1949.

[8] French, L. A.: Bull. Univ. Minnesota Hospitals, 20: 18, 1949.

[9] Brit. Med. J.: 2: 920, 1948.

* N, N-Dimethyl-N′-benzyl-N′ (alpha-pyridyl) ethylene-diamine monohydrochloride.

The results obtained with the previously described routine are tabulated alongside the findings of Alyea and Haines for the purposes of comparing our "treated" group with the "untreated" group of the latter workers.

Incidence of General Reactions

	RECEIVED ANTI-HISTAMINIC DRUG PROPHYLAXIS	ALYEA & HAINES (NO DRUG PROPHYLAXIS)
Control group (negative allergic history and negative sensitivity test reactions)	None	3.5%
Negative allergic history positive sensitivity test reactions	None	13.6%
Positive allergic history negative sensitivity test reactions	2 patients (5%)	10%
Positive allergic history positive sensitivity test reactions	8 patients (28%)	70%

In the group of 10 patients who experienced general reactions in this series, two of the patients exhibited severe responses. Both of these patients had "all-year-around" bronchial asthma and manifested positive conjunctival and intradermal sensitivity tests. There were no fatalities.

The idea has recently occurred to us that prophylactic antihistaminic therapy could be more effectively applied in patients with positive allergic histories and positive sensitivity test reactions by increasing the dosage of the drug and waiting two hours in order to obtain a higher blood level of the medications. Administration of the histamine antagonist by intramuscular injection might also accomplish the same purpose in shorter time.

Since the publication of original description of antihistaminic drug prophylaxis, Goldman[10] has reported favorable experiences without a single reaction in preparing patients for hysterosalpingography with pyribenzamine.

Essrig[11] has used the technique in preparing patients for cardiovascular roentgenologic studies during which time 40 cc diodrast was injected rapidly directly into the brachial vein; he did not observe a single general reaction to the diodrast with the prophylactic use of pyribenzamine.

SUMMARY

Excretory urography is not an innocuous procedure and may be responsible for reactions of variable severity including death. A genuine need for some means to protect patients against the complications of this otherwise simple and important diagnostic procedure must be sought.

Based on the premise that these reactions are fundamentally allergic responses to the contrast medium, it has been proposed that antihistaminic drugs be administered prophylactically before the dye is injected. The results obtained with this technique have been better than the usual experience with the "untreated" group. The discovery of a panacea to the entire problem of diodrast reactions is neither claimed nor implied. In the relatively small series of cases presented in this study, no final conclusions can be logically or fairly deduced. The appreciable reduction in reactions associated with excretory urography in patients who were previously fortified with antihistaminic drugs must surely justify further investigations into this type of prophylactic therapy.

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[10] Goldman, D.: Urol. & Cutan. Rev., 52: 606, 1948.
[11] Essrig, I. M.: New Eng. J. Med., 240: 15, 1949.

CONCLUSION

Antihistaminic drugs were administered to patients as a prophylaxis against reactions to the contrast medium used in excretory urography.

The results are encouraging and merit further study.

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GROSS HEMATURIA DUE TO DICUMAROL THERAPY

EUGENE S. GILMER AND LINUS W. HEWIT

Since 1942, numerous cases of hematuria due to dicumarol have been reported. Nichol[1] analyzed 9,000 cases in which anticoagulant therapy was employed, using data obtained from a questionnaire, and reviewed 8,000 cases in the literature. In these 17,000 cases in which anticoagulants were used, the incidence of hemorrhage was 6 or 7 per cent with major hemorrhage in approximately 2 per cent; 26 deaths were due to hemorrhage, 15 in the first series attributed to the use of the anticoagulant and 11 due to hemorrhage in the second series. This author mentioned 8 additional deaths attributable to anticoagulants. In his study of 1,686 postoperative cases in which dicumarol therapy was used, Allen[2] noted that minor hemorrhage consisting of epistaxis, hematuria, petechiae and ecchymoses occurred in 3.1 per cent. He also reported 2 deaths owing to hemorrhage which may have been caused by dicumarol. In a later series of 1,983 postoperative cases reported by this author and his associates, minor hemorrhage occurred in 3.4 per cent and serious bleeding in 1.8 per cent. Smith and Mulligan[3] reported that in their series of 2,353 cases hematuria occurred twice after dicumarol prophylaxis against venous thrombosis in women undergoing surgery.

In the last 3 years we have observed 6 cases of gross hematuria caused, in our opinion, by the therapeutic use of dicumarol. We present them in the belief that they merit the attention of other urologists. We also include in this series a case of pulmonary embolism in which dicumarol therapy was not followed by hematuria, but prolonged prothrombin time persisted for more than 2 weeks.

CASE REPORTS

Case 1. J. I. L., a white woman aged 63, was admitted to the Tampa Municipal Hospital on May 28, 1948 because of gross hematuria and thrombophlebitis of the left leg. Two weeks prior to admission she had been given 3 red capsules the first day, 2 the second and 1 each day thereafter until gross hematuria started 5 days before admission. The hematuria was accompanied by severe pain over the entire back and both flanks; it radiated to the lower part of the abdomen and to the epigastrium, simulating bilateral renal colic.

Tenderness was elicited in the right flank, the urine was deeply bloody, the blood pressure was 130/80, the blood count indicated mild anemia, and thrombophlebitis of the veins of the left leg was present. Because it was not known what drug had been given, and because the first prothrombin time was reported normal, cystoscopy with pyelograms was performed the day after admission. The

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Read at annual meeting, Southeastern Section, American Urological Association, Gulfport, Miss., February 4, 1950.

[1] Nichol, E. S., Falk, O. P. J., Meneely, G. R. and Hull, E.: Symposium on anticoagulant therapy and cardiovascular disease. Panel discussion. South. Med. J., **42:** 943–950, 1949.

[2] Allen, E. V.: The clinical use of anticoagulants; report of treatment with dicumarol in 1,686 postoperative cases. J. A. M. A., **134:** 323–329, 1947.

Allen, E. V., Hines, E. A., Jr., Kvale, W. F. and Barker, N. W.: The use of dicumarol as an anticoagulant: experience in 2,307 cases. Ann. Int. Med., **27:** 371–381, 1947.

[3] Smith, G. Van S. and Mulligan, W. J.: Dicumarol prophylaxis against venous thrombosis in women undergoing surgery. Surg., Gynec. & Obst., **86:** 461–464, 1948.

urine from the bladder was grossly bloody with a few small clots present. The vesical mucosa was normal, and blood was seen coming from both ureteral orifices. Roentgen examination of the kidneys, ureters and bladder gave no evidence of calculi. The pyelogram of the left kidney and ureter was normal. In the upper two thirds of the pelvis and superior calyx of the right kidney a homogeneous filling defect was demonstrated. It had the appearance of a blood clot or tumor (fig. 1, *A*).

On the day after admission, the prothrombin time was 82 seconds, and we then concluded the drug given before admission was dicumarol. Since hematuria was still profuse after cystoscopy, 25 mg. vitamin K (Synkayvite) was given intravenously, and 10 mg. was administered intramuscularly every 3 hours over a period of 2 days until 130 mg. was given. The urine was clear in 24 hours after the first dose of vitamin K. A second pyelogram on the right side was obtained prior to the patient's discharge from the hospital and was normal (fig. 1, *B*).

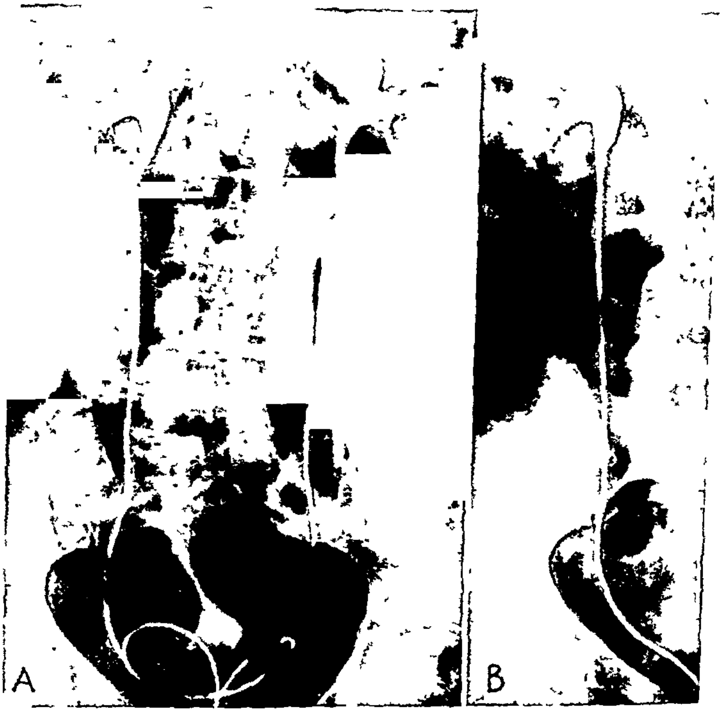

FIG. 1. Case 1. *A*, pyelogram showing homogeneous filling defect that gives appearance of blood clot or tumor in upper two thirds of pelvis and superior calyx of right kidney. *B*, normal pyelogram following vitamin K therapy.

Case 2. J. J. M., a white man aged 20, was admitted to the Tampa Municipal Hospital on July 22, 1949 because of thrombophlebitis of the left leg. He was given 1,800 mg. dicumarol over a period of 15 days. On the fourteenth day of dicumarol therapy, he had severe bilateral renal colic, pain over the entire abdomen, particularly in the epigastrium, and gross hematuria. The prothrombin time at this time was 1 minute and 21 seconds. The renal colic lasted 48 hours and required morphine for relief. The patient was given 50 mg. vitamin K

(Synkayvite) intravenously on August 9, and 30 mg. intravenously the following day. The renal colic promptly disappeared, the urine became clear within 48 hours, and the prothrombin time returned to normal without delay. This patient was given too much dicumarol from the start and should have received vitamin K therapy when the prothrombin time fell below 20 per cent of normal. He was a healthy young man, and therefore the response to vitamin K was prompt.

Case 3. L. M. T., a white man aged 72, was admitted to the Tampa Municipal Hospital on October 16, 1947 with symptoms of prostatism and acute urinary retention. After preliminary drainage by catheter, transurethral prostatic resection was performed with little hemorrhage, and the catheter was removed on the fourth postoperative day. On this date, the patient had a small pulmonary embolism which was first diagnosed as pleurisy, and on the tenth postoperative day definite thrombophlebitis of the veins of the left leg was noted. Immediately, bilateral ligation of the femoral vein was performed. Over a period of 7 days following the ligation, 600 mg. dicumarol was given, and on the seventh day of dicumarol therapy and the fourteenth postoperative day following transurethral prostatic resection, there developed gross hematuria, which persisted for 10 days. The urine was red in color, there were no clots, and it was not necessary to insert an indwelling catheter for its control. The prothrombin time was only slightly prolonged, and vitamin K therapy was not used. We do not believe that the hematuria was due to necrosis in the prostatic fossae.

Case 4. J. A. A., a white man aged 67, was admitted to the Tampa Municipal Hospital on February 4, 1947 with an acute anterior myocardial infarction confirmed by electrocardiogram. Acute urinary retention developed shortly after admission, and an 18F Foley catheter was inserted into the bladder. A total of 700 mg. dicumarol was given over a period of 5 days. Gross hematuria began on the fifth day of therapy and continued for 12 days, being excessive for 4 days. The prothrombin time at the onset of hematuria was 1 minute and 5 seconds. On February 14, 10 days after the hematuria started, the prothrombin time was 6 minutes and 54 seconds. The patient was given 25 mg. vitamin K (Synkayvite) intravenously. On February 18, when the prothrombin time had become more prolonged, bleeding became excessive, and the patient went into shock. At that time, 50 mg. vitamin K was given intravenously, followed by 10 mg. intramuscularly every 4 hours for 6 doses. Bleeding subsided 48 hours after the large dose of vitamin K was given intravenously.

Daily prothrombin time determinations were obtained and were reported normal 5 days prior to cysto-urethroscopic examination, which was performed on February 24. The cysto-urethroscopic examination at that time revealed that the vesical mucosa was inflamed throughout. There was considerable oozing from the wall of the bladder, and an area of ulceration at the vesical neck bled freely. A grade 2 enlargement of the median and lateral lobes of the prostate was present, and the prostatic bed appeared nodular and pearly white. A diagnosis of carcinoma of the prostate with ulceration in the prostatic urethra was made. The prostate was hard, nodular and fixed per rectum. Following the cysto-urethroscopic examination on February 25, there was considerable hemorrhage for 48 hours, but it was controlled by 25 mg. vitamin K given intravenously. The patient was discharged 1 week later.

In this case, even when a small dose of dicumarol had been given, the prothrombin time was so prolonged that it was difficult to bring it within normal limits with vitamin K therapy. Also, considerable hemorrhage continued for 48 hours even though the prothrombin time had been normal for 5 days prior to cysto-urethroscopic examination. If we had used larger doses of vitamin K in the beginning, we believe the results would have been much better.

Case 5. J. W. W., a white man aged 70, was admitted to the Tampa Municipal Hospital on November 12, 1947 because of acute urinary retention due to benign prostatic hyperplasia. An indwelling catheter was inserted. On the fourteenth day after admission thrombosis of the right femoral vein developed, and bilateral ligation of the femoral vein was performed. Over a period of 4 days, 700 mg. dicumarol was given orally. The prothrombin time 4 days after cessation of dicumarol therapy was 1 minute and 51 seconds, and 10 mg. vitamin K (Synkayvite) was given intramuscularly every 4 hours for 5 days, a total of 300 mg. On December 9, eleven days after dicumarol was discontinued, the prothrombin time was reported normal, and transurethral prostatic resection was performed. All prostatic tissue was resected, and bleeding was profuse and not entirely controlled when the patient left the operating table. Hemorrhage from the urethra continued for 20 days postoperatively. It required 1,500 cc blood in divided doses to keep up the hemoglobin and red blood cell count. Few blood clots were seen in the urine following the operation, but the urine was red in color during this time. Postoperatively, the patient was given 10 mg. vitamin K intramuscularly every 4 hours for 8 days, a total of 480 mg. When he was discharged on the twenty-sixth day after the operation, the urine was clear.

Bleeding was profuse for 20 days after transurethral resection in spite of normal prothrombin time before surgery. Vitamin K was given as directed in the literature at that time. We realize now that the amount was entirely inadequate and that this vitamin should have been given in much larger doses intravenously. There may have been hepatic damage or renal insufficiency which was not recognized. This case illustrates that when an ulcerative lesion of the urinary tract is present, it may bleed for 20 days. We think this bleeding was caused by dicumarol.

Case 6. B. F. H., a white man aged 78, was admitted to the Tampa Municipal Hospital on February 23, 1948 with acute urinary retention due to benign prostatic hyperplasia and a large left scrotal hernia. On February 27, herniorrhaphy was performed on the left side, and on March 5, thrombophlebitis developed in the left leg. Over a period of 7 days before and following ligation of the right femoral vein, 1,200 mg. dicumarol was given.

Eight days after the last dose of dicumarol was administered, the prothrombin time was reported normal, and transurethral prostatic resection was performed. After resection of 10 gm. tissue generalized oozing developed and became so profuse that it was necessary to stop the operation. Red urine oozed for 7 days, necessitating frequent irrigations, and the indwelling catheter was not removed until the eighth postoperative day. A second transurethral resection was performed 15 days following the first resection, and again bleeding at the time of operation was profuse, but the urine cleared in 48 hours. The prothrombin time was reported normal prior to the second resection. The patient was discharged 8 days after the second resection.

He returned to the hospital 2 months later with severe jaundice and died as a result of pathologic changes in the liver. No vitamin K therapy was given to this patient. We do not know why there was bleeding following the first resection when the prothrombin time was reported normal.

Case 7. W. W. G., a white man aged 86, was admitted to St. Joseph's Hospital on April 19, 1947 with a diagnosis of pulmonary embolism, probably due to thrombosis in the pelvic veins. After admission he was incontinent of urine, and a retention catheter was inserted. Over a period of 3 days, 600 mg. dicumarol was given. Hematuria did not develop, but it is interesting to note that the prothrombin time remained prolonged for a period of 15 days in spite of vitamin K (Synkayvite) therapy. Only 10 mg. of the vitamin was given twice a day for 5 days. This patient was senile and debilitated and may have had renal or hepatic damage. These factors probably account for the prolonged prothrombin time which continued over a period of 15 days. In view of our previous experience with dicumarol, we thought that prostatic surgery should be postponed.

DISCUSSION

The first 2 cases reported illustrate the typical symptoms of bilateral renal colic which may occur in cases of hematuria caused by dicumarol. Also, they particularly stress the unusual feature of pain referred to the epigastrium when bilateral renal colic is present. In both of these cases the patient obviously received an overdose of dicumarol and responded favorably to vitamin K therapy. The patient was, however, in good physical condition in both instances.

It is now known that the amounts of vitamin K which were recommended and first used were entirely inadequate. According to Allen,[3] 30 to 60 mg. vitamin K injected intravenously should be used when hemorrhage due to dicumarol is present. Had we used larger doses in the beginning and given them intravenously, we probably would not have had the difficulty encountered with this drug. One need fear no ill effects from large doses of vitamin K as Heindl, Anderson and Friedlander[4] reported a case in which the patient received 585.6 mg. hykinone intravenously over a period of 8 days with no unfavorable results.

In debilitated patients, it seems to take 7 to 21 days for the body to eliminate all the effects of dicumarol. Rosenbloom and Crane[5] reported a case in which hematuria persisted 14 days after withdrawal of dicumarol. They used synthetic vitamin K in large amounts to control the hemorrhage, but this therapy proved ineffective.

Falk[1] concluded *that the use of dicumarol is contraindicated* in the presence of hepatic damage, renal disease and blood dysoriasias, following operations on the central nervous system, and when there is a history of gastro-intestinal hemorrhage in the past, active peptic ulcer, menorrhagia or bloody stools from any source in the recent past. From our experience we believe that dicumarol *should not be used when a urethral catheter is necessary or when there is any* ulcerative lesion of the urinary tract. It should not be used when any type of prostatectomy is contemplated. If the drug has been used prior to prostatectomy, a period of at least 21 days should elapse before surgery.

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[4] Heindl, I. A., Anderson, B. G. and Friedlander, R. D.: Acute idiopathic hypoprothrombinemia, response to massive doses of vitamin K. Ann. Int. Med., 29: 347–356, 1948.

[5] Rosenbloom, D. and Crane, J. J.: Massive hematuria due to dicumarol overdosage. J. A. M. A., 132: 924–925, 1946.

SUMMARY

Hematuria following the use of dicumarol is not uncommon. Seven cases are reported, in 6 of which gross hematuria followed therapy with this drug. In the seventh case the prothrombin time was prolonged for 15 days despite vitamin K therapy.

When gross hematuria due to dicumarol is present, vitamin K should be given intravenously in large doses.

Dicumarol probably should not be administered when an indwelling catheter is necessary or when prostatectomy by any method is contemplated.

Gross hematuria may persist for a period of 7 to 21 days following dicumarol therapy if an ulcerative lesion of the urinary tract is present.

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